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Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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ABSTRACT

Introduction: Routine inpatient care (RIC) for cancer patients forms various pathways of clinical procedures. Although most of the individual procedures comprising the pathways have been tested via clinical trials, little is known about the collective cost-effectiveness of the pathways as a whole. This study aims at identifying pathways of RIC procedures for lung cancer patients from rural Anhui, China and examining determinants of the pathways and their links to cost-effectiveness.

Methods and analysis: The study adopts a retrospective cohort study design and proceeds in 5 steps. Step 1 defines 4 main categories of study variables including clinical procedures, direct cost and effectiveness of procedures, and factors affecting use of these procedures and their cost and effectiveness. Step 2 selects a cohort of 5000 lung cancer patients diagnosed between July 1, 2014 and June 30, 2015 from rural Anhui by clustered-random sampling. Step 3 retrieves the records of all the inpatient care episodes due to the lung cancer and extracts data about RIC procedures, proximate patient outcomes (e.g., Karnofsky performance status, lung function score) and related factors (e.g., stage of cancer, age, gender) by 2 independent clinician researchers using a pre-developed worksheet. Step 4 estimates the direct cost of each of the RIC procedures using micro-costing and collects data about ultimate patient outcomes (survival and progression-free survival) through a follow up survey of patients and/or their close relatives. Step 5 analyzes data collected and explores pathways of RIC procedures and their relations with patient outcomes, costs, cost-effect ratios and a whole range of clinical and socio-demographic factors using multivariate regression and path models.

Ethics and dissemination: The study protocol has been approved by authorized ethics committee. Findings from the study will be disseminated through conventional academic routes such as peer-reviewed publications and presentations and regional, national and international conferences.

Trial registry

ISRCTN25595562

Key words: cost effectiveness, lung cancer, inpatient care, retrospective study, China

Strengths and limitations of this study

- The study adopts a retrospective cohort study design involving a large representative sample of community patients;
- It evaluates cost-effectiveness of pathways of clinical procedures as a whole rather than individual procedures;
- It examines pathways of routine inpatient care for a huge but understudied Chinese rural population;
- It extracts data from routine records kept at different hospitals and thus suffers from discrepancies in performances and data qualities.

Introduction

Lung cancer has been the most common cancer in the world for several decades.¹ Estimated new cases of the disease was 1.8 million in 2012 (12.9% of the total), 58% of which occurred in less developed regions. Lung cancer was also the most common cause of death from cancer worldwide, being responsible for nearly one in five (1.59 million in absolute number) of the total.² In China, lung cancer incidence shows a slight decreasing trend in the past few years, particularly for males. However, it is still the top first cancer for males and second for females, accounting for 25.2% of all new cancer cases and 29.5% of all cancer deaths in 2012.³

Routine inpatient care (RIC) for lung cancer consists of a combination of procedures. Patients with possible lung cancer need a detailed history and physical examination first. Then they should undergo posterior-anterior and lateral chest radiographs as well as CT scans of the chest and abdomen. In order to further confirm and determine stage and histology of the lesion, other diagnostic methods needed include whole-body fluoro-deoxy-glucose positron emission tomography, endoscopic ultrasound, sputum cytology, fine-needle aspiration, bronchoscopy and others. Following diagnosis of lung cancer, the patients proceed with combined-modality therapies depending on stage of the disease and co-morbidity and complications. Historically, surgery provides the best chance for cure for patients whose lung cancers are limited to the hemithorax and can be totally encompassed by excision.^{4 5} And surgery has been generally used in combination with external-beam radiotherapy for control of the primary tumor and regional lymphatics.⁶ In addition, chemotherapy has also been advocated as an integral part of combined modality approaches to earlier stages of disease.^{7 8} For unselected advanced none-small cell lung cancer, platinum-based combinations have become the standard of care; while cisplatin- or carboplatin-based doublets are standard for patients with stage IV disease.^{9 10} More recently, EGFR tyrosine kinase inhibitors have been introduced in second- and third-line treatment of advanced disease and in first-line treatment for selected patients.¹¹

Given the complex procedures, ensuring quality RIC for lung cancer patients has been most challenging and guidelines are widely used in addressing this challenge. Numerous

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3 studies have documented positive relations between compliance with guidelines and
4 patients outcomes.^{12 13} However, researchers also have raised concerns about guidelines.
5 One of such concerns refers to lack of adequate consideration of costs. Most clinical
6 procedures not only affect disease outcomes but also incur considerable costs.^{14 15} Yet
7 guidelines are based on trials focused primarily on effectiveness (e.g., survival) with little
8 attention being paid to economic consequences.¹⁶ Another concern relates to
9 incompatible population between clinical trials and RIC. Clinical trials on which
10 guidelines are based use highly selected populations; while RIC serves a general lung
11 cancer population with different age, performance status and comorbidities.^{17 18} A third
12 concern revolves uncertain interactions between procedures. Although most individual
13 guideline recommended procedures (GRPs) have established evidences, they are not used
14 in isolation but in conjunction with others forming various clinical pathways. Efforts
15 systematically assessing and comparing these pathways are scarce.¹⁹⁻²² A fourth concern
16 originates from varied compliance with guidelines since RIC often deviates substantially
17 from guidelines.^{23 24} The cost-effectiveness of these “substandard” pathways or mixed
18 combinations of procedures (partly from guidelines, partly from experiences of
19 individual clinicians) falls far from well-understood.²⁵ These all points to a conclusion
20 that guidelines may not necessarily secure expected outcomes and there is a clear need
21 for monitoring RIC.
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29 All the above mentioned concerns surrounding cancer care are most pertinent to China.
30 First, China has a unique “dual” medical care system in which patients often receive
31 western medical medicine and traditional Chinese medicine simultaneously or in turn.²⁶
32 Second, China lacks coordinated referral and follow up mechanisms and cancer patients
33 often moves freely from one hospital to another for different rounds of inpatient care.²⁷
34 This makes it hard for clinicians in leveraging different inpatient care episodes at
35 different time points and hospitals into continuous and synergetic service. Third, China
36 has strong socio-cultural norms and financial incentives that hinder cost control and
37 guideline compliance.²⁸
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41 **Study aims**

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43 This study aims at identifying pathways of RIC procedures for lung cancer patients from
44 rural Anhui, China and examining determinants of the pathways and their links to cost-
45 effectiveness.
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48 **Methodology**

49 **Guiding framework**

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51 The study uses a retrospective cohort design. Content of the study is defined using a
52 practical framework as depicted by Figure 1. The framework holds that: a) patient
53 outcomes and costs jointly define the ultimate goal, cost-effectiveness, of RIC; b) clinical
54 procedures affect final patient outcomes indirectly via modifying psycho-physio-
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3 pathological factors of patient outcomes and incur costs simultaneously; c) decision-
4 making determines selection of RIC procedures based on understanding and prediction of
5 the status of all the other elements included in the framework. By excluding the two
6 brown circles, Figure 1 becomes an outcome-oriented framework that represents typical
7 current RIC for cancer patients. Given that all clinical procedures inevitably incur more
8 or less cost which in turn directly or/and indirectly affects selection and implementation
9 of clinical procedures, cost-effectiveness oriented approaches are more relevant than
10 outcomes-focused ones.²⁹

14 **Identification of procedures**

15 The study uses a self-designed data extraction form in identifying major clinical
16 procedures described in any RIC record under concern. The form lists all major RIC
17 procedures under two main domains, i.e., diagnostic procedures (e.g., chest X-ray, chest
18 CT, neck ultrasonography; Part D of supplementary file 1) and treatment procedures (e.g.,
19 surgical therapy, chemotherapy, psycho-behavioral intervention; Part E of supplementary
20 file 1).

24 **Estimation of costs**

25 The study estimates overall and categorical costs (direct costs only) for each of the RIC
26 procedures (e.g., lung function examination, computed tomography, white blood cell
27 count) identified above using micro-costing techniques.³⁰ Taking the example of lung
28 function examination, categorical costs include costs on personnel, equipment, materials,
29 regents and others need in completing the examination; while overall cost of the
30 procedure equals the sum of all these categorical costs. In addition, the study also
31 calculates overall cost on individual inpatient by adding up the overall costs on all the
32 clinical procedures he/she has received.

37 **Measurement of effectiveness**

38 The study uses both proximate outcome (PO) and ultimate outcome (UO) measures of
39 effectiveness of RIC procedures. The UO indicators derive from a follow up survey
40 about 2 years and half after the first hospitalization and include survival and progression-
41 free survival (PFS). The PO measures come from RIC records and include Eastern
42 Cooperative Oncology Group (ECOG), Karnofsky performance status (KPS) and
43 compiled scores of: a) symptoms (e.g., chronic cough, chest pain, wasting syndrome); b)
44 lung functions (e.g., forced vital capacity, forced one second expiratory volume), c)
45 image findings (e.g., number of nodules identified in the lung, size of the largest nodules,
46 presence of pleura or pericardial effusion); d) biological test findings (e.g., value of CEA,
47 CA125, proGRP); and e) complications and comorbidities (e.g., presence of superior
48 vena cava syndrome, superior vena cava syndrome). Each of these domain specific PO
49 scores equals weighted sum of all sub-indicators within the domain. For example, the
50 compiled score of “lung functions” equals the sum of weighted values of forced vital
51 capacity, forced one second expiratory volume etc. Here the weights come from the
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3 coefficients of multivariate regression modeling using an UO indicator (e.g., survival) as
4 the dependent variable; while forced vital capacity, forced one second expiratory volume
5 etc. as the independent variables; and stage of disease, age, gender and others as the
6 confounding variables.
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8 9 **Calculation of cost-effectiveness**

10 The study adopts cost-effectiveness ratios (CERs) and incremental cost-effectiveness
11 ratio (ICERs) as the main indicator for measuring cost-effectiveness. Here ICER is
12 defined by the difference in cost between two possible set of RIC procedures, divided by
13 the difference in their effect. More specifically, $ICER = (C_1 - C_0)/(E_1 - E_0)$, where
14 C_1 and E_1 is the cost and effect in the study group and C_0 and E_0 , the cost and effect in the
15 reference group.³¹ ICER represents the average incremental cost associated with 1
16 additional unit of the measure of effect. It serves a useful rule in resource allocation or
17 clinical decision-making.³²
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22 **Identification of influencing factors**

23 The study also extracts, from RIC records, data about patient factors commonly believed
24 to be linked with disease progression, treatment response and outcomes and utilization of
25 RIC procedures. These include socio-demographics (e.g., age, gender, body height and
26 weight, education, employment, marital status, medical insurance), risk behaviors and
27 histories (e.g., smoking, alcohol drinking, history of cancer among family members), and
28 clinical characteristics (e.g., stage of disease, historical findings, biomarkers).
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32 **Selection of participants**

33 The study is implemented in Anhui, an inland province located in middle and east China.
34 It has a population of 61.4 million and its per capita GDP and income rank in the middle
35 (14th) among all provinces in the nation.^{33 34} The social, cultural and economic
36 background of Anhui is representative of over 80% of the whole population in China.^{33 34}
37 The province has 68 rural counties and each of them divides into 10 to 20 townships.
38 Selection of participating counties, townships, patients and RIC case records uses a
39 clustered random sampling which proceeds in 5 steps. Step 1 classifies all the counties in
40 Anhui into southern, northern and middle areas. Step 2 randomly selects 3 counties from
41 each of these areas (12 counties in total). Step 3 randomly draws 4 townships from each
42 of the counties selected (48 townships in total). Step 4 searches the provincial
43 reimbursement database of the New Rural Medical System (NRMS) and identifies all the
44 patients within the selected townships who had been first diagnosed with primary lung
45 cancer during July 1, 2014 and June 30, 2015. Step 5 searches the database again for all
46 episodes of hospitalization due to the lung cancer for the patients identified in step 4.
47 NRMS covers 98% of the rural residents and the estimated number of patients and
48 admission episodes is about 5,000 and 25,000 respectively.
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Data collection

The study obtains data through follow-up survey and data extraction. The follow-up survey applies to all the lung cancer patients identified above. It solicits information about the patient's: a) disease progression (i.e., died, alive with or without progression); b) if died, date of death; c) additional admissions due to the lung cancer not included in the above mentioned NRMS database. The survey uses a short structured questionnaire (supplementary file 2). Administration of the questionnaire starts with a telephone interview (of the patient under concern or his/her close relatives for up to 5 time attempts) followed by a face-to-face interview (of the same respondents for up to 2 attempts) if the telephone contacts failed. The data extraction applies to records of all the hospital admission episodes identified via the NRMS database and the follow up survey. It uses a structured form (supplementary file 1) and extracts data about the clinical procedures, costs, effectiveness and influencing factors described above. Two experienced clinicians on care of lung cancer perform the data extraction. They visit (on one-by-one base) all the relevant hospitals, ask for permission to examine the full records and fill the worksheet independently first followed by discussions, if applicable, to solve discrepancies.

Data analysis

The data collected above allow a variety of descriptive and multivariate analysis. In particular, the data analysis centers on effectiveness, costs and pathway-based cost-effectiveness of RIC. Effectiveness analysis comprises mainly: a) description of UO indicators (e.g., survival rate) at different time points after first diagnosis by disease stage, age range etc. (Figure 2); b) multivariate regression models using UO indicators as dependent and socio-demographics, disease stage, selected RIC procedures and others as independent variables; c) path models using similar independent variables in b as exogenous, PO indices as direct endogenous, and UP indicators as indirect endogenous variables.

Similarly, cost analysis includes mainly: a) description of overall and categorical costs on different rounds of hospitalization by socio-demographic and selected clinical conditions (Figure 3); b) scatter plot of RIC procedures using the occurrence rate and unit cost of individual procedures as the coordinates; and c) multivariate models of overall and selected categorical costs.

Pathway-based cost-effectiveness analysis focuses primarily on constructing a pathway tree showing different combinations of RIC procedures starting from the first to the last episode of inpatient care and estimated cost-effectiveness ratios (CERs/ICERs) for each branches of the tree (Figure 4). It also performs multivariate regression analysis exploring potential factors affecting the flow of RIC among different branches.

Ethics and dissemination

The study involves retrieving RIC records and recruiting patients or their relatives. So it adheres to rigorous human subject protection principles. The study protocol had been reviewed and approved by the Biomedical Ethics Committee of Anhui Medical University (reference number: 20170312). Participation of hospitals, patients and their relatives are voluntary and written informed consent is sought from all participants. Findings from the study will be disseminated through conventional academic routes such as peer-reviewed publications and presentations and regional, national and international conferences.

Discussion

This study addresses RIC for lung cancer at hospitals in China from a range of meaningful perspectives. The study reinforces the concepts introduced in the landmark studies of Fisher et al and Wennberg et al, which convincingly demonstrated that high quality was not necessarily associated with high cost.³⁵ Describing inpatient lung cancer care in a view that its value is directly proportional to outcomes and inversely proportional to costs helps in guiding quality improvement by either better outcomes and/or lower costs.³⁶ The study calculates and compares the collective cost-effectiveness of different RIC pathways as a whole and thus informs coordinated inpatient care episodes and procedures at different time points and hospitals. The study enables ICERs estimation for specific guideline recommended procedures (GRPs) using various combinations of real and uncontrollable RIC procedures as the reference and thus enhances understanding and application of GRPs established through well-controlled studies in routine practice contexts.

Perhaps the most noteworthy findings of the current study may be the description of the pathways of RIC procedures and their links with cost-effectiveness (Figure 4). These pathways will provide easily understandable means for estimating and identifying, among others, the following: a) which pathways or combinations of procedures happen most or least in routine practice during different rounds of hospitalization for inpatients suffering from lung cancer in rural China; b) which pathways (from the first to last round of hospitalization) incur the highest or lowest direct costs; c) which pathways result in the best or worst patient outcome in terms of different PO and UO measures; d) which pathways are most or least cost-effective in terms of e.g., per unit cost gains in PFS, KPS, symptoms, lung functions, image findings, biological test findings, complications and comorbidities. These have important implications for clinical decision-making as well as policy-making.

Another point worth mentioning in particular refers to the links between the domain specific proximate outcome (PO) indices to key ultimate outcome (UO) indicators (e.g., survival) generated via a large scale (involving 5000 lung cancer patients) retrospective

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3 cohort study. They provide useful references for clinicians on care of lung cancer patients
4 in selecting appropriate procedures to achieve optimal collective contributions to UO.³⁷
5 At present, although PO indicators are routinely observed, they are presented to
6 clinicians as individual indicators rather than compiled indices. And given the large
7 number of PO indicators involved and the complex relations between RIC procedures
8 and PO indicators and then UO indicators, it is difficult for practicing clinicians to make
9 balanced decisions upon their personal experiences.³⁸
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13 The study also has limitations. First, different hospitals use different equipment, reagents
14 and medicines. Their quality of case records may also vary substantially. These raise
15 compatibility concerns in pooling data from different hospitals together and performing
16 aggregate analysis. Second, the study considers only inpatient care; while patients may
17 use various self-treatment and outpatient treatment in addition to inpatient care.^{39 40} And
18 inpatient and non-inpatient treatment may substitute each other to some extent. These
19 may result in under-estimation of the effectiveness of RIC procedures. Third, more severe
20 or complicated cases of lung cancer patients may be more likely to use inpatient care.
21 This may again lead to false reduced efficacy of inpatient care. Fourth, study uses only
22 direct costs rather than full costs taking both direct and indirect costs into consideration.
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27 **Competing interests**

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30 The authors declare no competing interests.
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32 **Authors' contributions**

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35 XS and MD contributed equally in conceiving this project, facilitating protocol and
36 instrument development, and drafting this manuscript. RF, ML, PZ and TJ are core
37 researchers for cost estimation, record extraction, follow up survey and data analysis
38 respectively. DW provided expertise for overall design of the study, and revised and
39 finalized the manuscript. All authors have read and approved the final submission.
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3 Figure 1 Guiding framework for cost-effectiveness evaluation
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5 Figure 2 Simulated survival after first diagnosis of lung cancer
6

7 Figure 3 Simulated cost by selected socio-demographics and clinical characteristics
8 (TC=total cost; KRMB=1000 Chinese yuan)
9

10 Figure 4 Anticipated “procedure-outcome” tree of inpatient lung cancer care (Tx = the
11 xth round of hospitalization; Cx = the xth combination of clinical procedures; Px =
12 possibility of using the xth combinations of clinical procedures; Ox = the xth patient
13 outcome index/indicator)
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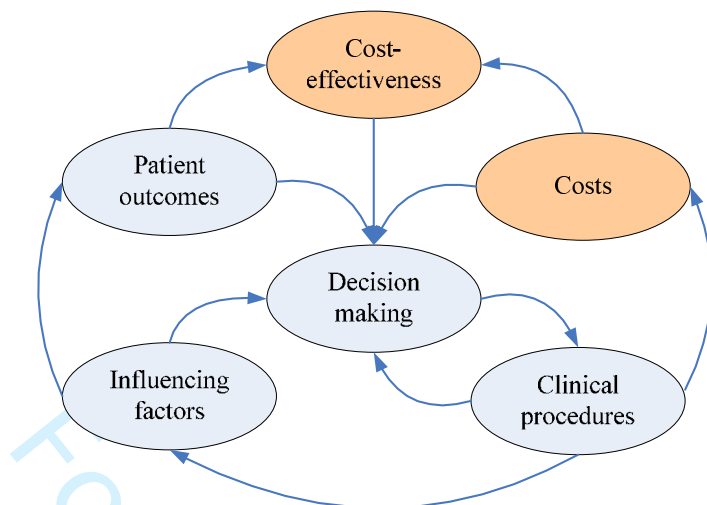


Figure 1 Guiding framework for cost-effectiveness evaluation

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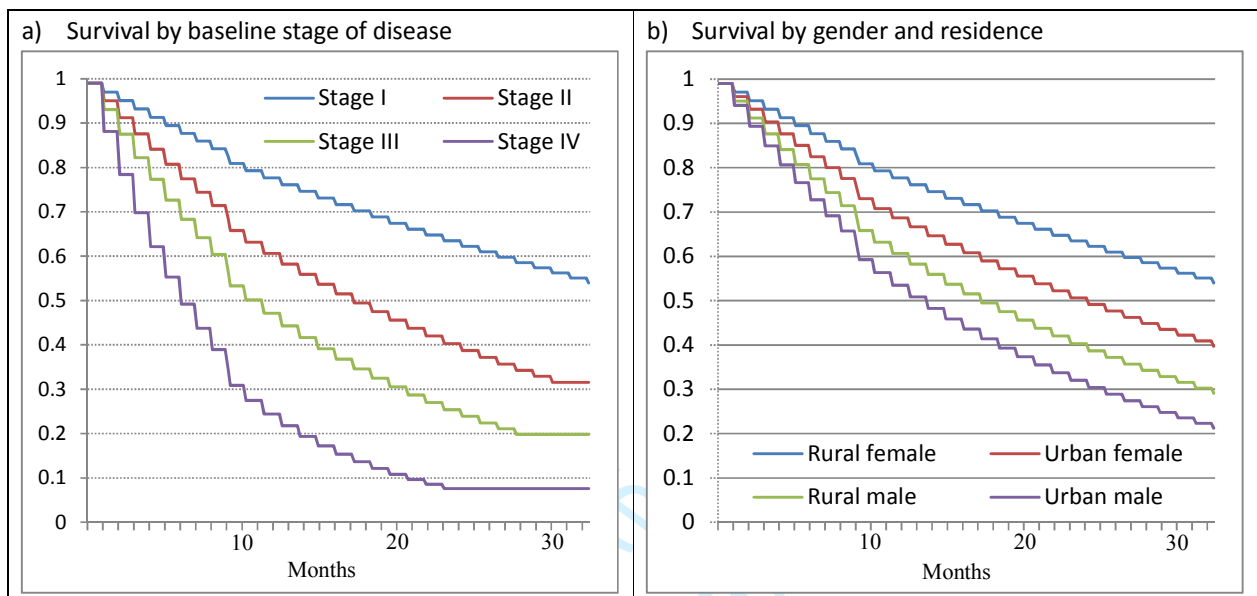


Figure 2 Simulated survival after first diagnosis of lung cancer

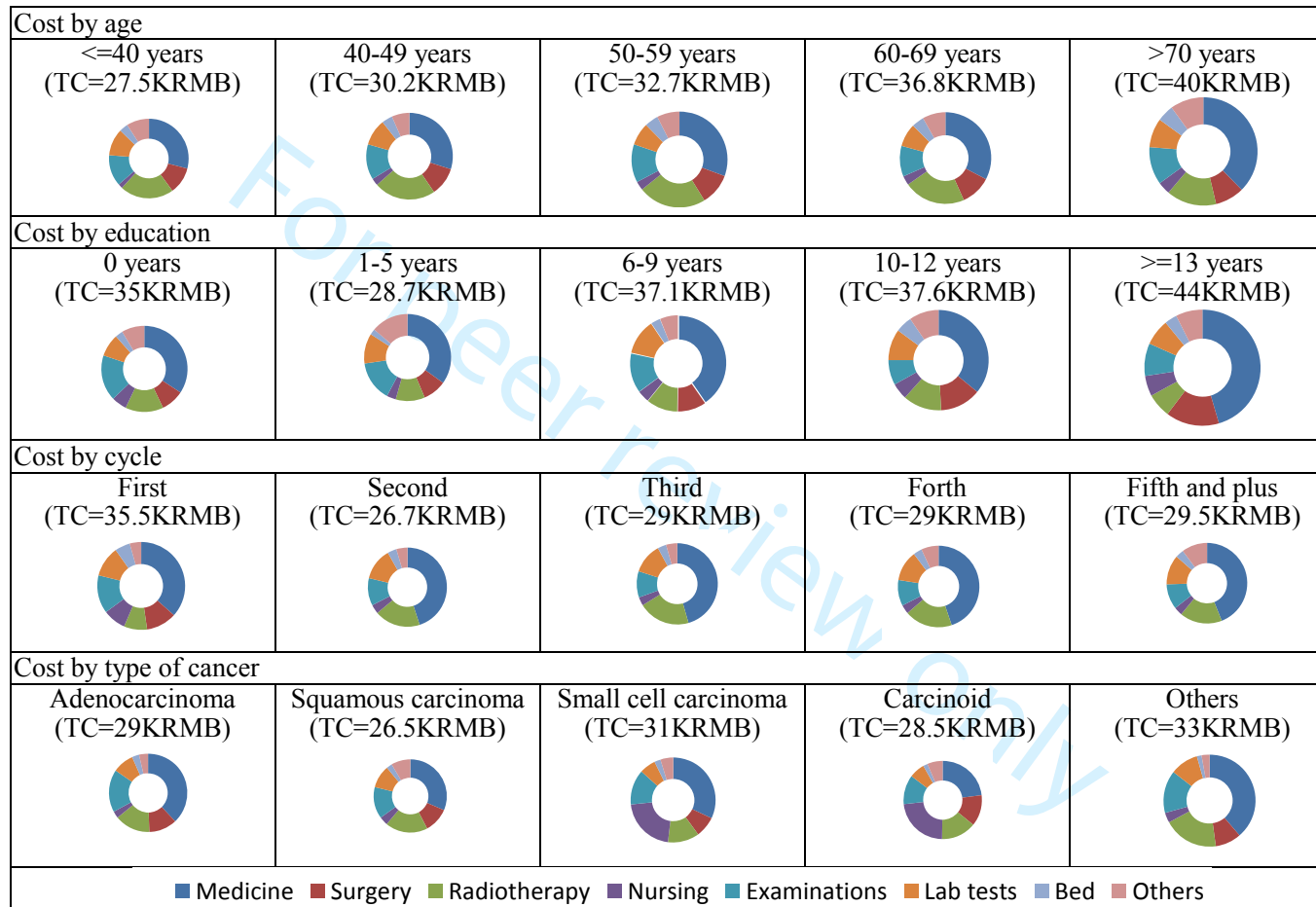


Figure 3 Simulated cost by selected socio-demographics and clinical characteristics (TC=total cost; KRMB=1000 Chinese yuan)

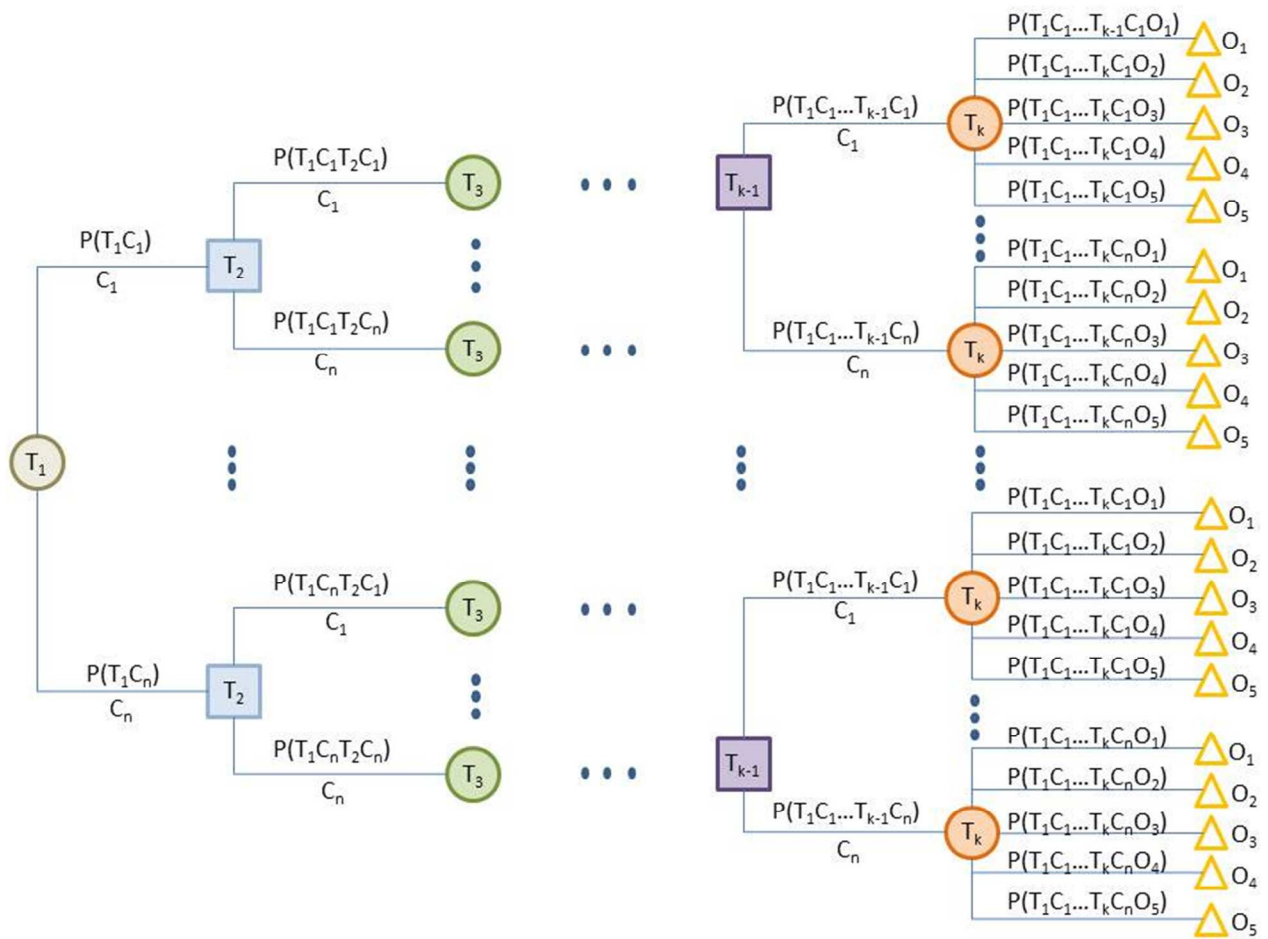


Figure 4 Anticipated “procedure-outcome” tree of inpatient lung cancer care (T_x = the x^{th} round of hospitalization; C_x = the x^{th} combination of clinical procedures; P_x = possibility of using the x^{th} combinations of clinical procedures; O_x = the x^{th} patient outcome index/indicator)

Annex 1 Lung cancer inpatient care data extraction form

Reference Number: -

Part A: Patient's social demographics

1.1 Case record number:

1.2 Patient identification number:

1.3 Sex: [1]Male [2]Female

1.4 Birth date (dd-mm-yyyy, first case record only): --

1.5 Body height (centimeter, first case record only):

1.6 Body weight (kilogram):

1.7 Education (first case record only):

- | | | |
|-------------------------|--------------------|------------------------|
| [1] No formal education | [2] Primary school | [3] Middle school |
| [4] High school | [5] College | [6] Graduate or higher |
| [9] Not clear | | |

1.8 Occupation (first case record only):

- | | | |
|------------------------------|-----------------------|-------------------|
| [1] Staff of public entities | [2] Employee of firms | [3] Self-employed |
| [4] Peasant | [5] Un-employed | [6] Retired |
| [7] Army member | [9] Not clear | |

1.9 Marital status:

- | | | |
|---------------|-------------|---------------|
| [1] Unmarried | [2] Married | [3] Divorced |
| [4] Widowed | [5] Other | [9] Not clear |

1.10 Medical insurance:

- [1] Essential medical insurance for urban employees
- [2] Medical insurance for urban citizens
- [3] New rural cooperative medical care systems
- [4] Commercial medical insurance
- [5] Public medical care system
- [6] Out-of-pocket care
- [7] Other
- [9] Not clear

Part B: Patient's behavior and disease history (first case record only)

2.1 Smoking:

- | | | |
|-----------------------------|-------------------|----------------|
| [1] Current smoker | [2] Former smoker | [3] Non-smoker |
| [9] Not clear (skip to 2.2) | | |

2.1.1 Number of cigarettes smoked per day:

2.1.2 Number of years smoked:

2.1.3 Number of years ceased smoking:

2.2 Previous diagnosis of the following respiratory diseases:

- [1] Tuberculosis [2] Chronic bronchitis [3] Emphysema
 [4] Asthma [5] Silicosis/pneumoconiosis
 [6] Other(specify)

2.3 Previous diagnosis of the following cardio-cerebrovascular/endocrine diseases:

- [1] Hypertension [2] Coronary heart disease [3] Cerebral thrombosis
 [4] Cerebral hemorrhage [5] Hyperlipemia [6] Diabetes
 [7] Other(specify)

2.4 Previous diagnosis of cancer (enter location of cancer, if applicable, e.g., breast cancer, colorectal cancer)

- [1] [2] [3]
 [4] [5] [6]
 [7] [8] [9]

(Please add more cells as needed)

2.5 Previous diagnosis of cancer among relatives

Number	Type of relatives	Location of cancer
[1]		
[2]		
[3]		

(Please add more rows as needed)

Part C: Patient's current symptoms/signs

3.1 Respiratory symptoms/signs

- [1] Chronic coughing [2] Sputum with blood [3] Chest suppression
 [4] Chest pain [5] Difficult breathing [6] Repeated bronchitis
 [7] Hoarseness [8] Other (specify)
 [9] None

3.2 Symptoms/signs of metabolism or immunity dysfunction:

- [1] None [2] Hippocratic fingers/toes [3] Amyasthenia
 [4] Hyponatremia [5] Blacken skin folds
 [6] Other (specify)

3.3 Symptoms/signs relating to lung cancer metastasis:

- [1] None [2] Topical pain [3] Headache
 [4] Dizzy [5] Sudden dyskinesia [6] Facial swelling
 [7] Other (specify)

3.4 Cancer-related non-specific symptoms/signs:

- [1] None [2] Apparent emaciation [3] Weakness
 [4] Mild/moderate fever [5] Other (specify)

3.5 Karnofsky score:

- [1]
 [2] Not available

3.6 Body surface examination findings:

- [1] None

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2
3 [2] Enlargement of lymph nodes in the neck or supraclavicular region
4 [3] Lymph node enlargement in other areas
5 [4] Subcutaneous nodule
6 [5] Horner syndrome
7 [6] Facial swelling
8 [7] Other (specify)
9 [9] Not clear
10
11
12

13 Part D: Diagnostic procedures and findings

14 4 Imaging diagnosis

15 4.1 Chest X-ray examination:

16 [1] Not performed (skip to 4.2)

17 [2] Performed

18 4.1.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

19 4.1.2 Abnormalities identified

20 [1] None

21 [2] Pulmonary nodules/mass

22 [3] Hilar / mediastinal abnormalities

23 [4] Pleural effusion

24 [5] Pericardial effusion

25 [6] Other (specify)

26 4.1.2.1 If [2], please specify the largest nodules/mass: |_|_|.|_|*|_|_|.|_|cm

27 4.2 Chest CT examination:

28 [1] Not performed (skip to 4.3)

29 [2] Performed

30 4.2.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

31 4.2.2 Type of CT performed

32 [1] Plain

33 [2] Enhanced scan

34 [3] Plain + enhanced

35 4.2.3 Layer thickness: |_|_|.|_|cm

36 4.2.4 Multiple plane reconstruction (MPR):

37 [1] Yes [2] No

38 4.2.5 Locations scanned

39 [1] Chest

40 [2] Chest and abdomen

41 [3] Neck and chest

42 [4] Neck+chest+abdomen

43 4.2.6 Abnormalities identified

44 4.2.6.1 Diagnosis from chest CT

45 [1] No abnormalities

46 [2] Affirmative benign

47 [3] Suspected benign

48 [4] Suspected malignant [5] Affirmative malignant

49 [6] Others (specify)

50 [9] Not clear

51 4.2.6.2 Abnormalities identified

- 1
2
3 [1] Pneumonia [2] Bronchial abnormality [3] Single nodules/mass
4 [4] Multiple nodules/mass [5] Pleural effusion [6] Pericardial effusion
5 [7] Other (specify)
6 4.2.6.2.1 If [3] or [4], size of the largest nodules/mass: |_|_|.|_|*|_|_|.|_|cm
7
8 4.3 Head CT examination:
9 [1] Not performed (skip to 4.4)
10 [2] Performed
11 4.3.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|
12 4.3.2 Type of CT performed
13 [1] Plain [2] Enhanced scan [3] Plain + enhanced
14 4.3.3 Diagnosis from head CT
15 [1] No abnormalities [2] Confirmed/suspected brain metastases
16 [3] Others (specify)
17
18 4.4 Head MR examination
19 [1] Not performed (skip to 4.5)
20 [2] Performed
21 4.4.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|
22 4.4.2 Diagnosis from head MR
23 [1] No abnormalities [2] Single brain metastases [3] Multiple brain metastases
24 [4] Others (specify)
25 4.4.2.1 If [2] or [3], size of the largest nodules/mass: |_|_|.|_|*|_|_|.|_|cm
26
27 4.5 Chest MR examination
28 [1] Not performed (skip to 4.6)
29 [2] Performed
30 4.5.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|
31 4.5.2 Diagnosis from chest MR
32 [1] No abnormalities [2] Hilar/mediastinal lymph nodes [3] Lung nodules/mass
33 [4] Bone metastases [5] Thoracic/pericardial effusion
34 [6] Others (specify)
35 4.5.2.1 If [3], size of the largest nodules/mass: |_|_|.|_|*|_|_|.|_|cm
36 4.5.2.2 If [4], location metastases
37
38 4.6 Bone MR examination
39 [1] Not performed (skip to 4.7)
40 [2] Performed
41 4.6.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|
42 4.6.2 Diagnosis from bone MR
43 [1] No abnormalities [2] Bone metastases
44 [3] Others (specify)
45 4.6.2.1 If [2], location of metastases
46
47 4.7 Neck ultrasonography
48 [1] Not performed (skip to 4.8)
49 [2] Performed
50 4.7.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|
51 4.7.2 Diagnosis from neck ultrasonography
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- [1] No abnormalities [2] Neck /supraclavicular lymph nodes
[3] Others (specify)

4.8 Chest ultrasonography

- [1] Not performed (skip to 4.9)
[2] Performed

4.8.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4.8.2 Diagnosis from chest ultrasonography

- [1] No abnormalities [2] Pleural effusion [3] Pericardial effusion
[4] Others (specify)

4.9 Abdominal ultrasonography

- [1] Not performed (skip to 4.10)
[2] Performed

4.9.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4.9.2 Diagnosis from abdominal ultrasonography

- [1] No abnormalities [2] Liver metastases [3] Adrenal gland transfer
[4] Peritoneal/retroperitoneal lymphadenopathy
[5] Others (specify)

4.10 Bone scans

- [1] Not performed (skip to 4.11)
[2] Performed

4.10.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4.10.2 Diagnosis from bone scans

- [1] No abnormalities [2] confirmed metastases [3] Suspected metastases
[4] Others (specify)

4.10.2.1 If [2] or [3], location of metastases

4.11 PET-CT examination

- [1] Not performed (skip to 5.1)
[2] Performed

4.11.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4.11.2 Diagnosis from PET-CT examination

- [1] No abnormalities [2] Lung nodules/mass(Primary lesion)
[3] Pulmonary metastasis [4] Lymph node metastasis
[5] Adrenal gland transfer [6] Bone transfer
[7] Other site transfer [8] Thoracic / pericardial effusion
[9] Others (specify)

4.11.3.1 If [2], location of lung nodules/mass

4.11.3.1.1 Size of the largest nodules/mass: |_|_|.|_|*|_|_|.|_|cm

4.11.3.1.2 SUV

4.11.3.1.3 Nature of the nodules/mass identified:

- [1] Affirmative benign [2] Suspected benign [3] Suspected malignant
[4] Affirmative malignant [5] Not clear [6] Others (specify)

4.11.3.2 If [3], location of pulmonary metastasis

4.11.3.2.1 SUV

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3 4.11.3.3 If [4], location of lymph node metastasis
4 4.11.3.3.1 SUV
5 4.11.3.4 If [5], location of adrenal gland metastasis
6 4.11.3.4.1 SUV
7
8 4.11.3.5 If [6], location of bone metastases
9 4.11.3.5.1 SUV
10 4.11.3.6 If [7], location of other metastases
11 4.11.3.6.1 SUV
12
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14 5 Endoscopic examinations

15 5.1 Fiberoptic bronchoscopy

16 [1] Not performed (skip to 5.2)

17 [2] Performed

18 5.1.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|_|

19 5.1.2 Diagnosis from fiberoptic bronchoscopy

20 [1] No abnormalities [2] Tumor

21 [3] Others (specify)

22 [4] Not clear

23 5.2 Lavage cytology/brushing

24 [1] Not performed (skip to 5.3)

25 [2] Not clear (skip to 5.3)

26 [3] Performed

27 5.2.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|_|

28 5.3 Bronchoscopy clamp biopsy

29 [1] Not performed (skip to 5.4)

30 [2] Not clear (skip to 5.4)

31 [3] Performed

32 5.3.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|_|

33 5.4 Bronchoscopy aspiration biopsy

34 [1] Not performed (skip to 5.5)

35 [2] Not clear (skip to 5.5)

36 [3] Performed

37 5.4.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|_|

38 5.4.2 Type of bronchoscopy aspiration biopsy

39 [1] Endobroncheal ultrasonography [2] Electromagnetic-guided

40 [3] Transbronchial needle aspiration [4] Not clear

41 [5] Others (specify)

6 Laboratory/biological tests

6.0 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.1 CEA

[1] Not performed (skip to 6.2)

[2] Not clear (skip to 6.2)

[3] Performed

6.1.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.1.2 Test result (value-unit): _____ - _____

6.2 CA125

[1] Not performed (skip to 6.3)

[2] Not clear (skip to 6.3)

[3] Performed

6.2.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.2.2 Test result (value-unit): _____ - _____

6.3 proGRP

[1] Not performed (skip to 6.4)

[2] Not clear (skip to 6.4)

[3] Performed

6.3.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.3.2 Test result (value-unit): _____ - _____

6.4 SCC

[1] Not performed (skip to 6.5)

[2] Not clear (skip to 6.5)

[3] Performed

6.4.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.4.2 Test result (value-unit): _____ - _____

6.5 NSE

[1] Not performed (skip to 6)

[2] Not clear (skip to 6.6)

[3] Performed

6.5.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.5.2 Test result (value-unit): _____ - _____

6.6 CYFRA21-1

[1] Not performed (skip to 6.7)

[2] Not clear (skip to 6.7)

[3] Performed

6.6.1 Date of performance if different from 6.0

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3 (dd-mm-yyyy): |__|__|-|__|__|-|__|__|__|__|
4 6.6.2 Test result (value-unit): _____ - _____
5 6.7 WBC
6 [1] Not performed (skip to 6.8)
7 [2] Not clear (skip to 6.8)
8 [3] Performed
9 6.7.1 Date of performance if different from 6.0
10 (dd-mm-yyyy): |__|__|-|__|__|-|__|__|__|__|
11 6.7.2 Test result (value-unit): _____ - _____
12 6.8 PLT
13 [1] Not performed (skip to 6.9)
14 [2] Not clear (skip to 6.9)
15 [3] Performed
16 6.8.1 Date of performance if different from 6.0
17 (dd-mm-yyyy): |__|__|-|__|__|-|__|__|__|__|
18 6.8.2 Test result (value-unit): _____ - _____
19 6.9 Hb
20 [1] Not performed (skip to 6.10)
21 [2] Not clear (skip to 6.10)
22 [3] Performed
23 6.9.1 Date of performance if different from 6.0
24 (dd-mm-yyyy): |__|__|-|__|__|-|__|__|__|__|
25 6.9.2 Test result (value-unit): _____ - _____
26 6.10 ALB
27 [1] Not performed (skip to 6.11)
28 [2] Not clear (skip to 6.11)
29 [3] Performed
30 6.10.1 Date of performance if different from 6.0
31 (dd-mm-yyyy): |__|__|-|__|__|-|__|__|__|__|
32 6.10.2 Test result (value-unit): _____ - _____
33 6.11 Pre-ALB
34 [1] Not performed (skip to 6.12)
35 [2] Not clear (skip to 6.12)
36 [3] Performed
37 6.11.1 Date of performance if different from 6.0
38 (dd-mm-yyyy): |__|__|-|__|__|-|__|__|__|__|
39 6.11.2 Test result (value-unit): _____ - _____
40 6.12 Ca
41 [1] Not performed (skip to 6.13)
42 [2] Not clear (skip to 6.13)
43 [3] Performed
44 6.12.1 Date of performance if different from 6.0
45 (dd-mm-yyyy): |__|__|-|__|__|-|__|__|__|__|
46 6.12.2 Test result (value-unit): _____ - _____
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6.13 Fe

[1] Not performed (skip to 6.14)

[2] Not clear (skip to 6.14)

[3] Performed

6.13.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.13.2 Test result (value-unit): _____ - _____

6.14 FIB

[1] Not performed (skip to 6.15)

[2] Not clear (skip to 6.15)

[3] Performed

6.14.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.14.2 Test result (value-unit): _____ - _____

6.15 D-D

[1] Not performed (skip to 6.16)

[2] Not clear (skip to 6.16)

[3] Performed

6.15.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.15.2 Test result (value-unit): _____ - _____

6.16 Na

[1] Not performed (skip to 6.17)

[2] Not clear (skip to 6.17)

[3] Performed

6.16.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.16.2 Test result (value-unit): _____ - _____

6.17 LDL

[1] Not performed (skip to 6.18)

[2] Not clear (skip to 6.18)

[3] Performed

6.17.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.17.2 Test result (value-unit): _____ - _____

6.18 LDL

[1] Not performed (skip to 6.19)

[2] Not clear (skip to 6.19)

[3] Performed

6.18.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

6.18.2 Test result (value-unit): _____ - _____

6.19 TG

- [1] Not performed (skip to 6.20)
- [2] Not clear (skip to 6.20)
- [3] Performed

6.19.1 Date of performance if different from 6.0

(dd-mm-yyyy): --

6.19.2 Test result (value-unit): _____ - _____

6.20 TCHOL

- [1] Not performed (skip to 7.1)
- [2] Not clear (skip to 7.1)
- [3] Performed

6.20.1 Date of performance if different from 6.0

(dd-mm-yyyy): --

6.20.2 Test result (value-unit): _____ - _____

7 Heart and lung function examinations

7.1 Electrocardiogram examination

- [1] Not performed (skip to 7.2)
- [2] Performed

7.1.1 Date of performance (dd-mm-yyyy): --7.1.2 Heart rate: times/minutes

7.1.3 Diagnosis from electrocardiogram examination

- [1] No abnormalities
- [2] Abnormalities(specify)

7.2 Lung function examinations

- [1] Not performed (skip to 8.1)
- [2] Not clear (skip to 8.1)
- [3] Performed

7.2.1 Date of performance (dd-mm-yyyy): --

7.2.2 FVC (Tested/predicted value): _____ / _____

7.2.3 FEV1(Tested/predicted value): _____ / _____

7.2.4 FEV1/FVC%(Tested/predicted value): _____ / _____

7.2.5 TLCO SB(Tested/predicted value): _____ / _____

7.2.6 Ventilation function assessment:

- | | | |
|----------------------|--------------------|------------------------|
| [1] No abnormalities | [2] Mildly reduced | [3] Moderately reduced |
| [4] Severely reduced | [5] Restrictive | [6] Obstruction |
| [7] Mixed | [8] Not clear | |

7.2.7 Lung capacity

- [1] No abnormalities
- [2] Increased total residue ratio
- [3] Low lung capacity
- [4] Not clear

7.2.8 Breath diffusion

- [1] No abnormalities
- [2] Reduced
- [3] Not clear

8 Histological/cytological examination

8.1 Preoperative cytological

[1] Not performed (skip to 8.2)

[2] Not clear (skip to 8.2)

[3] Performed

8.1.1 If [3], preoperative cytological method:

[1] Needle biopsy [2] Sputum specimen examination [3] Bronchial lavage

[4] Others (specify)

8.1.2 If [3], preoperative cytological result:

[1] With cancer cells [2] Without cancer cells [3] Uncertain lesion

[4] Not clear

8.1.2.1 If [1], cytological type

[1] Adenocarcinoma [2] Squamous cell carcinoma

[3] Small cell carcinoma [4] Carcinoid

[5] Large cell carcinoma [6] Squamous cell carcinoma

[7] Sarcomatoid carcinoma [8] carcinoma from sialaden

[9] Not clear [10] Others (specify)

8.1.2.1.1 If [1], first class subtype code

[1] Pre-invasion lesion [2] Microinvasive adenocarcinoma

[3] Invasive adenocarcinoma [4] Variant invasive adenocarcinoma

[5] Others (specify)

[6] Not clear

8.1.2.1.1.1 If [1], second class subtype code

[1] Atypical adenocarcinoma like hyperplasia

[2] Adenocarcinoma in situ

[6] Not clear

8.1.2.1.1.2 If [3], second class subtype code

[1] Accumbens dominated [2] Acinar dominated

[3] Papillary dominated [4] Micro papillae dominated

[5] Entities with mucus dominated

[6] Not clear

8.1.2.1.1.3 If [4], second class subtype code

[1] Mucinous invasive adenocarcinoma

[2] Colloid [3] Fetal

[4] Intestinal [5] Others (specify)

[6] Not clear

8.2 Preoperative histological

[1] Not performed (skip to 10.4)

[2] Not clear (skip to 10.4)

[3] Performed

8.2.1 If [3], method of preoperative histological biopsy:

[1] Ultrasound guided aspiration biopsy [2] CT guided aspiration biopsy

[3] Bronchoscopic biopsy [4] Nuclear magnetic puncture

- 1
2
3 [5] Not clear [6] Others (specify)
4 8.2.1.1 If [3], results of preoperative histological biopsy:
5 [1] With cancer cells [2] Without cancer cells [3] Uncertain lesion
6 [4] Not clear
7
8 8.2.2.1 If [1], histological type:
9 [1] Adenocarcinoma [2] Squamous cell carcinoma
10 [3] Small cell carcinoma [4] Carcinoid
11 [5] Large cell carcinoma [6] Squamous cell carcinoma
12 [7] Sarcomatoid carcinoma [8] carcinoma from sialaden
13 [9] Not clear [10] Others (specify)
14
15 8.2.2.1.1.1 If [1], second class subtype code
16 [1] Atypical adenocarcinoma like hyperplasia
17 [2] Adenocarcinoma in situ
18 [6] Not clear
19
20 8.2.2.1.1.2 If [3], second class subtype code
21 [1] Accumbens dominated [2] Acinar dominated
22 [3] Papillary dominated [4] Micro papillae dominated
23 [5] Entities with mucus dominated
24 [6] Not clear
25
26 8.2.2.1.1.3 If [4], second class subtype code
27 [1] Mucinous invasive adenocarcinoma
28 [2] Colloid [3] Fetal
29 [4] Intestinal [5] Others (specify)
30 [6] Not clear
31
32 8.2.2.2 If 8.2.2.1 information not available, please tick in histology type:
33 [1] Small cell lung cancer [2] Non-small cell lung cancer [3] Benign lesion
34 [4] Not clear [5] Others (specify)
35
36 8.3 Biopsy of frozen mass:
37 [1] Not performed (skip to 8.4)
38 [2] Not clear (skip to 8.4)
39 [3] Performed
40
41 8.3.1 If [3], diagnosis of frozen mass biopsy:
42 [1] Adenocarcinoma [2] Squamous cell carcinoma
43 [3] Small cell carcinoma [4] Carcinoid
44 [5] Large cell carcinoma [6] Squamous cell carcinoma
45 [7] Sarcomatoid carcinoma [8] carcinoma from sialaden
46 [9] Not clear [10] Others (specify)
47
48 8.3.2.1.1.1 If [1], second class subtype code
49 [1] Atypical adenocarcinoma like hyperplasia
50 [2] Adenocarcinoma in situ
51 [6] Not clear
52
53 8.3.2.1.1.2 If [3], second class subtype code
54 [1] Accumbens dominated [2] Acinar dominated
55 [3] Papillary dominated [4] Micro papillae dominated
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3 [5] Entities with mucus dominated
4 [6] Not clear
5 8.3.2.1.1.3 If [4], second class subtype code
6 [1] Mucinous invasive adenocarcinoma
7 [2] Colloid [3] Fetal
8 [4] Intestinal [5] Others (specify)
9 [6] Not clear
10
11 8.4 Biopsy of lymph node:
12 [1] Not performed (skip to 8.5)
13 [2] Not clear (skip to 8.5)
14 [3] Performed
15 8.4.1 If [3], result of lymph node biopsy:
16 [1] Metastasis [2] No metastasis
17
18 8.5 Biopsy of frozen margin of bronchus:
19 [1] Not performed (skip to 8.6)
20 [2] Not clear (skip to 8.6)
21 [3] Performed
22 8.5.1 If [3], result of frozen margin of bronchus:
23 [1] Margin tumor [2] No margin tumor
24
25
26 8.6 Postoperative histological
27 [1] Not performed (skip to 9)
28 [2] Not clear (skip to 9)
29 [3] Performed
30 8.6.1 If [3], number of tumors:
31 [1] Solitary tumor [2] More than 2 nodules [3] Not clear
32 8.6.1.1 The largest tumor size: **cm
33 8.6.1.2 If multiple tumor, the smallest tumor size: **cm
34
35 8.6.2 Pathologic diagnosis
36 [1] Adenocarcinoma [2] Squamous cell carcinoma
37 [3] Small cell carcinoma [4] Carcinoid
38 [5] Large cell carcinoma [6] Squamous cell carcinoma
39 [7] Sarcomatoid carcinoma [8] carcinoma from sialaden
40 [9] Not clear [10] Others (specify)
41
42 8.6.2.1 If [1], second class subtype code
43 [1] Atypical adenocarcinoma like hyperplasia
44 [2] Adenocarcinoma in situ
45 [6] Not clear
46 8.6.2.1.1 If [3], second class subtype code
47 [1] Accumbens dominated [2] Acinar dominated
48 [3] Papillary dominated [4] Micro papillae dominated
49 [5] Entities with mucus dominated
50 [6] Not clear
51 8.6.2.1.2 If [4], second class subtype code
52 [1] Mucinous invasive adenocarcinoma
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3 [2] Colloid [3] Fetal
4 [4] Intestinal [5] Others (specify)
5 [6] Not clear
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7 8.6.3 Differentiation degree:
8 [1] Well differentiated [2] Well and moderately differentiated
9 [3] Moderately differentiated [4] Poorly differentiated
10 [5] Middle and low differentiation [6] Undifferentiated
11 [7] Not clear
12
13 8.6.4 Associated with intrapulmonary metastasis
14 [1] Yes [2] No (skip to 10.11) [3] Not clear(skip to 10.11)
15 10.10.1 Invasion of pleura?
16 [1] Yes [2] No [3] Not clear
17
18 8.6.4.1 Invasion of the main bronchi?
19 [1] Yes, distance is less than 2cm [2] Yes, distance is more than 2cm
20 [3] No [3] Not clear
21
22 8.6.4.2 Invasion of chest wall/septum/mediastinum/pericardium?
23 [1] Yes(specify) [2] No [3] Not clear
24 8.6.4.3 Invasion of mediastinum/heart/trachea/esophagus/vertebral body/carina?
25 [1] Yes(specify) [2] No [3] Not clear
26
27 8.7 Resection margin positive?
28 [1] Not performed (skip to 10.6)
29 [2] Not clear (skip to 10.6)
30 [3] Positive
31 [4] Negative
32
33 8.8 The total number of lymph nodes detected
34 8.9 The total number of lymph node metastasis
35 8.10 Lymph node metastasis site
36 [1] No metastasis [2] Ipsilateral bronchi or hilum
37 [3] Ipsilateral mediastinum or carina [4] Contralateral mediastinum or hilum of lung, clavicle
38 [5] Not clear
39
40 9 Tumor marker
41 9.1 Her-2(C-erbB-2) detection
42 [1] Not performed (skip to 9.2)
43 [2] Not clear (skip to 9.2)
44 [3] Performed (skip to 9.2)
45 9.1.1 If [3], method of detection
46 [1] Immunohistochemistry [2] FISH [3] Other(Specify)
47 9.1.2 If [3], result of detection
48 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear
49
50 9.2 Anaplastic lymphoma kinase detection
51 [1] Not performed (skip to 9.3)
52 [2] Not clear (skip to 9.3)
53 [3] Performed (skip to 9.3)
54 9.2.1 If [3], method of detection
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3 [1] Immunohistochemistry [2] Genetic testing [3] Other(Specify)
4 9.2.2 If [3], result of detection
5 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear
6
7 9.3 Epidermal growth factor receptor detection
8 [1] Not performed (skip to 9.4)
9 [2] Not clear (skip to 9.4)
10 [3] Performed (skip to 9.4)
11 9.4.1 If [3], method of detection
12 [1] Immunohistochemistry [2] Genetic testing [3] Other(Specify)
13 9.3.2 If [3], result of detection
14 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear
15
16 9.4 K-ras detection
17 [1] Not performed (skip to 9.5)
18 [2] Not clear (skip to 9.5)
19 [3] Performed (skip to 9.5)
20 9.4.1 If [3], method of detection
21 [1] Immunohistochemistry [2] Gene mutation detection [3] Other(Specify)
22 9.4.2 If [3], result of detection
23 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear
24
25 9.5 Other factor types detection
26 [1] Not performed (skip to 9.6)
27 [2] Not clear (skip to 9.6)
28 [3] Performed (skip to 9.6)
29 9.6.1 If [3], method of detection
30 [1] Immunohistochemistry [2] Gene mutation detection [3] Other(Specify)
31 9.6.2 If [3], result of detection
32 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear
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38 9 Staging of lung cancer

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41 9.1 Type of staging available
42 [1] Clinical stage [2] Pathological staging [3] Not staging
43 [4] Not clear
44 9.2 Staging methods
45 [1] Clinical imaging [2] Pathological staging [3] Postoperative pathology
46 [4] No [5] Not clear
47
48 9.3 If staged, details of TNM staging
49 9.3.1 Staging system
50 [1] The 6th edition of UICC/AJCC staging, published in 2002
51 [2] The 7th edition of AHCC staging, published in 2009
52 9.3.2 T staging
53 [1] T1; [2] T2; [3] T3; [4] T4; [5] Tx; [6] Not clear
54 9.3.3 N staging
55 [1] N1; [2] N2; [3] N3; [4] N0; [5] Not clear
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9.3.4 M staging

[1] M1; [2] Mx; [3] M0; [4] Not clear

9.3.5 TNM staging

[1] Stage I; [2] Stage IIA; [3] Stage IIB; [4] Stage IIIA;
[5] Stage IIIB; [6] Stage IV; [7] Others (specify); [8] Not clear

9.4 Type of lung cancer:

[1] Small cell lung cancer [2] Non-Small cell lung cancer
[3] Mixed small cell lung cancer [4] Not clear
[5] Others (specify)

9.4.1 If [1], state of lesion

[1] Restricted [2] Pervasive
[3] Other (specify)

9.4.2 If [2], state of lesion

[1] Early stage [2] Locally advanced
[3] Advanced [4] Not clear

Part E: Treatment procedures and findings/results

9.1 Surgical treatment

[1] Not performed (skip to 9.2)
[2] Thoracotomy
[3] Video-assisted thoracoscopic surgery
[4] Thoracoscope assisted small incision surgery
[5] Others (specify)
[6] Not clear(skip to 9.2)

9.1.1 Details of resection:

[1] Lobectomy [2] Segmental resection
[3] Combined lobectomy [4] Completely pneumonectomy
[5] Sleeve lobectomy [6] Resection and reconstruction of carina
[7] Others (specify) [8] Not clear

9.1.1.1 If [2], name of the segment

9.1.1.2 If [4], treatment of pulmonary arteriovenous in pericardium

[1] Yes [2] No [3] Not clear

9.1.2 If [3], type of thoracoscope assistance:

[1] Single hole [2] Double holes [3] Three holes
[4] Multiple holes [5] Not clear

9.1.2.1 Conversion from video-assisted thoracoscopic surgery to Thoracotomy

[1] Yes [2] No [3] Not clear

9.1.3 Performance of rapid pathology

[1] Yes [2] No [3] Not clear

9.1.4 Findings from intraoperative exploration

9.1.4.1 Tumor site

[1] Left [2] Right [3] Upper lobes
[4] Bottom lobes [5] Middle lobes [6] Not clear

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3 9.1.4.2 Cross lobes
4 [1] Yes [2] No [3] Not clear
5 9.1.4.3 Pleural involvement/ Shrinkage
6 [1] Yes [2] No [3] Not clear
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8 9.1.4.4 Largest diameter of tumor: |_|_|.|_|_|cm
9 9.1.4.5 Pleural metastasis
10 [1] Yes [2] No [3] Not clear
11 9.1.4.6 Intrapulmonary metastasis
12 [1] Yes [2] No [3] Not clear
13 9.1.4.7 Foreign invasion
14 [1] Yes [2] No [3] Not clear
15 9.1.4.7.1 If [1], name of invaded tissue:
16 9.1.4.8 Dual(Multiple) primary tumor
17 [1] Yes [2] No [3] Not clear
18
19 9.1.5 Lymph node dissection
20 [1] Systematicness [2] Sampling [3] Not cleaned [4] Not Clear
21 9.1.6 Classification of surgery
22 [1] Radical cure [2] Palliative treatment [3] Not clear
23
24 9.2 Radiation therapy
25 [1] Not performed (skip to 9.3)
26 [2] Not clear (skip to 9.3)
27 [3] Performed
28 9.2.1 If [3], type of radiation therapy:
29 [1] Preoperative radiotherapy [2] Postoperative radiotherapy
30 [3] Radical radiation therapy
31 9.2.1.1 Combined with chemotherapy:
32 [1] Not performed (skip to 10.1.3)
33 [2] Not clear (skip to 10.1.3)
34 [3] Performed
35 9.2.1.1.1 If [3], type of chemo-radiotherapy:
36 [1] Sequence chemoradiotherapy [2] Concurrent chemoradiotherapy
37 9.2.1.1.2 If [2], name of the chemotherapy drugs
38 9.2.1.1.3 If [2], chemotherapy cycles:
39 [1] Every week [2] Biweekly [3] Every 3 weeks
40 [4] Every 4 weeks [5] Not clear
41 9.2.1.2 Radiotherapy technique
42 [1] Routine radiotherapy [2] Three-dimensional conformal radiotherapy
43 [3] Tomo treatment [4] Static intensity modulated radiotherapy
44 [5] Stereotactic radiotherapy [6] Rotational intensity modulated radiotherapy
45 [7] Not clear [8] Others (specify)
46 9.2.1.3 Polarization
47 [1] Conventional simulator [2] CT simulation [3] 4D-CT
48 [4] Not clear
49 9.2.1.4 Methods of pretreatment position verification
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- [1] No methods [2] Image guide radiation therapy
 [3] Not clear [4] Electronic Portal Imaging Device
 [5] Others (specify)

9.2.1.5 Radiation target area (multiple choice)

- [1] Primary foci [2] Postoperative stump and tumor bed
 [3] Involving lymph node irradiation [4] Choose lymph node irradiation
 [5] Metastatic lesions [6] Not clear

9.2.1.6 Radiotherapy dose division program

No	Radiation energy	Total dose Gy	Number of times	Treatment time (days)
[1]				
[2]				
[3]				

9.3 Chemotherapy

[1] Not performed (skip to 9.4)

[2] Not clear (skip to 9.4)

[3] Performed

9.3.1 If [3], type of chemotherapy:

[1] Neoadjuvant chemotherapy [2] Postoperative adjuvant chemotherapy

[3] Advanced chemotherapy [4] Others (specify)

9.3.1.1 If [1], neoadjuvant chemotherapy regimen

[1] Vinorelbine/Cisplatin+Vinorelbine/Carboplatin+Vinorelbine/Other platinum

[2] Paclitaxel/Cisplatin+Paclitaxel/Carboplatin+Paclitaxel/Other platinum

[3] Docetaxel/Cisplatin+ Docetaxel/Carboplatin +Docetaxel/Other platinum

[4] Pemetrexed/Cisplatin+Pemetrexed/Carboplatin+ Pemetrexed/Other platinum

[5] Gemcitabine/Cisplatin +Gemcitabine/Carboplatin +Gemcitabine/Other platinum

[6] Others (specify)

[7] Not clear

9.3.1.2 If [2], postoperative adjuvant chemotherapy regimen:

[1] Vinorelbine/Cisplatin+Vinorelbine/Carboplatin+Vinorelbine/Other platinum

[2] Paclitaxel/Cisplatin+Paclitaxel/Carboplatin+Paclitaxel/Other platinum

[3] Docetaxel/Cisplatin+Docetaxel/Carboplatin+Docetaxel/Other platinum

[4] Pemetrexed/Cisplatin+Pemetrexed/Carboplatin+Pemetrexed/Other platinum

[5] Gemcitabine/Cisplatin+Gemcitabine/Carboplatin+Gemcitabine/Other platinum

[6] Etoposide/Cisplatin+Etoposide/Carboplatin+Cyclophosphamide/Adriamycin/
 Vincristine

[7] Others (specify)

[8] Not clear

9.3.1.3 If [3], advanced chemotherapy regimen:

[1] Cisplatin+Carboplatin+Other platinum

[2] Paclitaxel+Docetaxel

[3] Gemcitabine

[4] Pemetrexed

[5] Vinorelbine+Vincristine

[6] Irinotecan+Topotecan

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3 [7] Tegafur
4 [8] Etoposide
5 [9] Cytosan+Ifosfamide
6 [10] Adriamycin
7 [11] Others(specify)
8 [12] Not clear
9
10 9.4 Complication treatment
11 9.4.1 Superior vena cava syndrome
12 [1] Not appeared(skip to 9.4.2) [2] Not clear(skip to 9.4.2) [3] Appeared
13 9.4.1.1 If [3], duration (month):
14 9.4.1.2 If [3], treatment:
15 [1] No (skip to 9.4.2) [2] Not clear(skip to 9.4.2) [3] Yes
16 9.4.1.2.1 If[3], treatment effect:
17 [1] Improved [2] Progressed [3] Stable [4] Not clear
18
19 9.4.2 Spinal cord compression syndrome
20 [1] Not appeared (skip to 9.4.3) [2] Not clear(skip to 9.4.3) [3] Appear
21 9.4.2.1 If [3], duration (month):
22 9.4.2.2 If [3], treatment:
23 [1] No (skip to 9.4.3) [2] Not clear(skip to 9.4.3) [3] Yes
24 9.4.2.2.1 If [3], treatment effect:
25 [1] Improved [2] Progressed [3] Stable [4] Not clear
26
27 9.4.3 Brain metastases
28 [1] Not appeared (skip to 9.4.4) [2] Not clear(skip to 9.4.4) [3] Appear
29 9.4.3.1 If [3], duration (month):
30 9.4.3.2 If [3], treatment:
31 [1] No (skip to 9.4.4) [2] Not clear(skip to 9.4.4) [3] Yes
32 9.4.3.2.1 If [3], treatment effect:
33 [1] Improved [2] Progressed [3] Stable [4] Not clear
34
35 9.4.4 Meningeal metastases
36 [1] Not appeared (skip to 9.4.5) [2] Not clear(skip to 9.4.5) [3] Appear
37 9.4.4.1 If [3], duration (month):
38 9.4.4.2 If [3], treatment:
39 [1] No (skip to 9.4.5) [2] Not clear(skip to 9.4.5) [3] Yes
40 9.4.4.2.1 If [3], treatment effect:
41 [1] Improved [2] Progressed [3] Stable [4] Not clear
42
43 9.4.5 Pleural effusion
44 [1] Not appeared (skip to 9.4.6) [2] Not clear(skip to 9.4.6) [3] Appear
45 9.4.5.1 If [3], duration (month):
46 9.4.5.2 If [3], treatment:
47 [1] No (skip to 9.4.6) [2] Not clear(skip to 9.4.6) [3] Yes
48 9.4.5.2.1 If [3], treatment effect:
49 [1] Improved [2] Progressed [3] Stable [4] Not clear
50
51 9.4.6 Pyoperitoneum
52 [1] Not appeared (skip to 9.4.7) [2] Not clear(skip to 9.4.7) [3] Appear
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3 9.4.6.1 If [3], duration (month):
4 9.4.6.2 If [3], treatment:
5 [1] No (skip to 9.4.7) [2] Not clear(skip to 9.4.7) [3] Yes
6
7 9.4.6.2.1 If [3], treatment effect:
8 [1] Improved [2] Progressed [3] Stable [4] Not clear
9
10 9.4.7 Pericardial effusion
11 [1] Not appeared(skip to 9.4.8) [2] Not clear(skip to 9.4.8) [3] Appear
12 9.4.7.1 If [3], duration (month):
13 9.4.7.2 If [3], treatment:
14 [1] No (skip to 9.4.8) [2] Not clear(skip to 9.4.8) [3] Yes
15 9.4.7.2.1 If [3], treatment effect:
16 [1] Improved [2] Progressed [3] Stable [4] Not clear
17
18 9.4.8 Intestinal obstruction
19 [1] Not appeared(skip to 9.4.9) [2] Not clear(skip to 9.4.9) [3] Appear
20 9.4.8.1 If [3], duration (month):
21 9.4.8.2 If [3], treatment:
22 [1] No (skip to 9.4.9) [2] Not clear(skip to 9.4.9) [3] Yes
23 9.4.8.2.1 If [3], treatment effect:
24 [1] Improved [2] Progressed [3] Stable [4] Not clear
25
26 9.4.9 Pain
27 [1] Not appeared (skip to 9.4.10) [2] Not clear(skip to 9.4.10) [3] Appear
28 9.4.9.1 If [3], duration (month):
29 9.4.9.2 If [3], treatment:
30 [1] No (skip to 9.4.10) [2] Not clear(skip to 9.4.10) [3] Yes
31 9.4.9.2.1 If [3], treatment effect (site and score):
32
33 9.4.10 Cerebral thrombosis/ hemorrhage
34 [1] Not appeared (skip to 9.4.11) [2] Not clear(skip to 9.4.11) [3] Appear
35 9.4.10.1 If [3], duration (month):
36 9.4.10.2 If [3], treatment:
37 [1] No (skip to 9.4.11) [2] Not clear(skip to 9.4.11) [3] Yes
38 9.4.10.2.1 If [3], treatment effect:
39 [1] Improved [2] Progressed [3] Stable [4] Not clear
40
41 9.4.11 Interstitial pneumonia
42 [1] Not appeared(skip to 9.4.12) [2] Not clear(skip to 9.4.12) [3] Appear
43 9.4.11.1 If [3], duration (month):
44 9.4.11.2 If [3], treatment:
45 [1] No (skip to 9.4.12) [2] Not clear(skip to 9.4.12) [3] Yes
46 9.4.11.2.1 If [3], treatment effect:
47 [1] Improved [2] Progressed [3] Stable [4] Not clear
48
49 9.4.12 Pulmonary embolism
50 [1] Not appeared(skip to 9.4.13) [2] Not clear(skip to 9.4.13) [3] Appear
51 9.4.12.1 If [3], duration (month):
52 9.4.12.2 If [3], treatment:
53 [1] No (skip to 9.4.13) [2] Not clear(skip to 9.4.13) [3] Yes
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3 9.4.12.2.1 If [3], treatment effect:
4 [1] Improved [2] Progressed [3] Stable [4] Not clear
5 9.4.13 Cardiac insufficiency
6 [1] Not appeared(skip to 9.4.14) [2] Not clear(skip to 9.4.14) [3] Appear
7 9.4.13.1 If [3], duration (month):
8 9.4.13.2 If [3], treatment:
9 [1] No (skip to 9.4.14) [2] Not clear(skip to 9.4.14) [3] Yes
10 9.4.13.2.1 If [3], treatment effect:
11 [1] Improved [2] Progressed [3] Stable [4] Not clear
12 9.4.14 Arrhythmia
13 [1] Not appeared(skip to 9.4.15) [2] Not clear(skip to 9.4.15) [3] Appear
14 9.4.14.1 If [3], duration (month):
15 9.4.14.2 If [3], treatment:
16 [1] No (skip to 9.4.15) [2] Not clear(skip to 9.4.15) [3] Yes
17 9.4.14.2.1 If [3], treatment effect:
18 [1] Improved [2] Progressed [3] Stable [4] Not clear
19 9.4.15 Hypercoagulable state
20 [1] Not appeared (skip to 9.5) [2] Not clear(skip to 9.5) [3] Appear
21 9.4.15.1 If [3], duration (month):
22 9.4.15.2 If [3], treatment:
23 [1] No (skip to 9.5) [2] Not clear(skip to 9.5) [3] Yes
24 9.4.15.2.1 If [3], treatment effect:
25 [1] Improved [2] Progressed [3] Stable [4] Not clear
26 9.5 Other procedures
27 9.5.1 Interdisciplinary consultation
28 [1] No (skip to 9.5.2) [2] Not clear(skip to 9.5.2) [3] Yes
29 9.5.1.1 Disciplines involved
30 [1] Neurology [2] Infectious diseases [3] Nephrology
31 [4] Endocrinology [5] Cardiovascular diseases
32 [6] Others (specify)
33 9.5.1.2 Total times of consultation:
34 9.5.2 Psychological/behavioral intervention
35 [1] No (skip to 9.5.3) [2] Not clear(skip to 9.5.3) [3] Yes
36 9.5.2.1 Type of interventions performed
37 [1] Neurology [2] Infectious diseases [3] Nephrology
38 [4] Endocrinology [5] Cardiovascular diseases
39 [6] Others (specify)
40 9.5.2.2 Total sessions of intervention performed:
41 9.5.3 Traditional Chinese medicine used
42 [1] No (skip to 10.1) [2] Not clear(skip to 10.1) [3] Yes
43 9.5.2.1 Regimen of TCM used (specify):
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45 9.5.2.2 Duration of TCM use (days):
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Part F: Charges on the inpatient care

10.1 Total inpatient care fee:

10.2 Registration fee

10.3 Bed fee

10.4 Examination fee

10.5 Treatment fee

10.6 Operation fee

10.7 Laboratory fee

10.8 Nursing fee

10.9 Medicines fee

10.10 Other fee

Name of data extractor:

Date of data extraction(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

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4. How are you (is he/she) now?

[1] Alive [2] Deceased

4.1. If [2], when did it happen (dd-mm-yyyy) ? |_|_|-|_|_|-|_|_|_|_|

5. In addition to the inpatient care and medical checkups mentioned above, have you (or has he/she) tried other measures to cure the lung cancer?

[1] Yes [2] No (skip to ending) [3] Not clear (skip to ending)

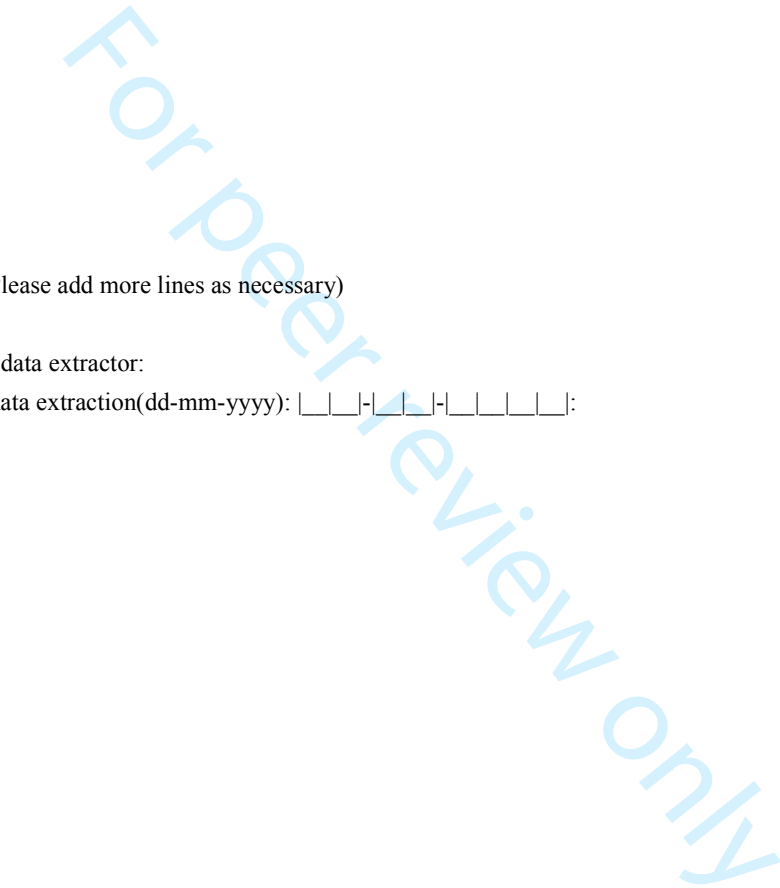
5.1. If yes, please tell me, one-by-one, what is it and how often it has/had been?

No.	Name of practice	Description of practice	Frequency	Length (months)
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Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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ABSTRACT

Introduction: Routine inpatient care (RIC) for cancer patients forms various pathways of clinical procedures. Although most of the individual procedures comprising the pathways have been tested via clinical trials, little is known about the collective cost-effectiveness of the pathways as a whole. This study aims at identifying pathways of RIC procedures for lung cancer patients from rural Anhui, China and examining determinants of the pathways and their links to cost-effectiveness.

Methods and analysis: The study adopts a retrospective cohort study design and proceeds in 5 steps. Step 1 defines 4 main categories of study variables including clinical procedures, direct cost and effectiveness of procedures, and factors affecting use of these procedures and their cost and effectiveness. Step 2 selects a cohort of 5000 lung cancer patients diagnosed between July 1, 2014 and June 30, 2015 from rural Anhui by clustered-random sampling. Step 3 retrieves the records of all the inpatient care episodes due to the lung cancer and extracts data about RIC procedures, proximate patient outcomes (e.g., Karnofsky performance status, lung function score) and related factors (e.g., stage of cancer, age, gender) by 2 independent clinician researchers using a pre-developed worksheet. Step 4 estimates the direct cost of each of the RIC procedures using micro-costing and collects data about ultimate patient outcomes (survival and progression-free survival) through a follow up survey of patients and/or their close relatives. Step 5 analyzes data collected and explores pathways of RIC procedures and their relations with patient outcomes, costs, cost-effect ratios and a whole range of clinical and socio-demographic factors using multivariate regression and path models.

Ethics and dissemination: The study protocol has been approved by authorized ethics committee. Findings from the study will be disseminated through conventional academic routes such as peer-reviewed publications and presentations and regional, national and international conferences.

Trial registry

ISRCTN25595562

Key words: cost effectiveness, lung cancer, inpatient care, retrospective study, China

Strengths and limitations of this study

- The study adopts a retrospective cohort study design involving a large representative sample of community patients;
- It evaluates cost-effectiveness of pathways of clinical procedures as a whole rather than individual procedures;
- It examines pathways of routine inpatient care for a huge but understudied Chinese rural population;
- It extracts data from routine records kept at different hospitals and thus suffers from discrepancies in performances and data qualities.

Introduction

Lung cancer has been the most common cancer in the world for several decades.¹ Estimated new cases of the disease was 1.8 million in 2012 (12.9% of the total), 58% of which occurred in less developed regions. Lung cancer was also the most common cause of death from cancer worldwide, being responsible for nearly one in five (1.59 million in absolute number) of the total.² In China, lung cancer incidence shows a slight decreasing trend in the past few years, particularly for males. However, it is still the top first cancer for males and second for females, accounting for 25.2% of all new cancer cases and 29.5% of all cancer deaths in 2012.³

Routine inpatient care (RIC) for lung cancer consists of a combination of procedures. Patients with possible lung cancer need a detailed history and physical examination first. Then they should undergo posterior-anterior and lateral chest radiographs as well as CT scans of the chest and abdomen. In order to further confirm and determine stage and histology of the lesion, other diagnostic methods needed include whole-body fluoro-deoxy-glucose positron emission tomography, endoscopic ultrasound, sputum cytology, fine-needle aspiration, bronchoscopy and others. Following diagnosis of lung cancer, the patients proceed with combined-modality therapies depending on stage of the disease and co-morbidity and complications. Historically, surgery provides the best chance for cure for patients whose lung cancers are limited to the hemithorax and can be totally encompassed by excision.^{4 5} And surgery has been generally used in combination with external-beam radiotherapy for control of the primary tumor and regional lymphatics.⁶ In addition, chemotherapy has also been advocated as an integral part of combined modality approaches to earlier stages of disease.^{7 8} For unselected advanced none-small cell lung cancer, platinum-based combinations have become the standard of care; while cisplatin- or carboplatin-based doublets are standard for patients with stage IV disease.^{9 10} More recently, EGFR tyrosine kinase inhibitors have been introduced in second- and third-line treatment of advanced disease and in first-line treatment for selected patients.¹¹

Given the complex procedures, ensuring quality RIC for lung cancer patients has been most challenging and guidelines are widely used in addressing this challenge. Numerous

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3 studies have documented positive relations between compliance with guidelines and
4 patient outcomes.^{12 13} However, researchers have also raised concerns about guidelines.
5 One of such concerns refers to lack of adequate consideration of costs. Most clinical
6 procedures not only affect disease outcomes but also incur considerable costs.^{14 15} Yet
7 guidelines are based on trials focused primarily on effectiveness (e.g., survival) with little
8 attention being paid to economic consequences.¹⁶ Another concern relates to
9 incompatible population between clinical trials and RIC. Clinical trials on which
10 guidelines are based use highly selected populations; while RIC serves a general lung
11 cancer population with different age, performance status and comorbidities.^{17 18} A third
12 concern revolves uncertain interactions between procedures. Although most individual
13 guideline recommended procedures (GRPs) have established evidences, they are not used
14 in isolation but in conjunction with others forming various clinical combinations. Efforts
15 systematically assessing and comparing these combinations are scarce.¹⁹⁻²² A fourth
16 concern originates from varied compliance with guidelines since RIC often deviates
17 substantially from guidelines.^{23 24} The cost-effectiveness of these “substandard” or mixed
18 combinations of procedures (partly from guidelines, partly from experiences of
19 individual clinicians) falls far from well-understood.²⁵ These all points to a clear need for
20 evaluating RIC even though guidelines are widely available.
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27 All the above mentioned concerns surrounding cancer care are most pertinent to China.
28 First, China has a unique “dual” medical care system in which patients often receive
29 western medicine and traditional Chinese medicine simultaneously or in turn.²⁶ Second,
30 China lacks coordinated referral and follow up mechanisms and cancer patients often
31 moves freely from one hospital to another for different rounds of inpatient care.²⁷ This
32 makes it hard for clinicians in leveraging different inpatient care episodes at different
33 time points and hospitals into continuous and synergetic service. Third, China has strong
34 socio-cultural norms and financial incentives that hinder cost control and guideline
35 compliance.²⁸
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41 **Study aims**

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43 This study aims at identifying pathways of RIC procedures for lung cancer patients from
44 rural Anhui, China and examining determinants of the pathways and their links to cost-
45 effectiveness. Specific questions to be addressed include: a) what combinations of
46 diagnosis and treatment procedures (or pathways for short) an individual patient may
47 experience during all his/her hospitalization episodes due to lung cancer-related problems;
48 b) what are the most and least frequent pathways; c) what determines the flow among
49 these pathways; d) how cost-effective is each of the pathways; and e) what factors are
50 associated with the cost-effectiveness.
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54 The above “pathways” of inpatient care means combinations of diagnosis and treatment
55 procedures an individual patient may experience during all his/her hospitalization
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3 episodes due to lung cancer-related problems. Suppose a lung cancer patient experienced
4 6 times/rounds of hospitalized care and during each of these hospitalization episodes, the
5 patient underwent several diagnosis and treatment procedures. Putting together, all these
6 procedures form the “pathway” of this particular patient.
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9 **Methodology**

10 **Identification of procedures**

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12 The study uses a self-designed data extraction form in identifying major clinical
13 procedures described in any RIC record under concern. The form lists all major RIC
14 procedures under two main domains, i.e., diagnostic procedures (e.g., chest X-ray, chest
15 CT, neck ultrasonography; Part D of supplementary file 1) and treatment procedures (e.g.,
16 surgical therapy, chemotherapy, psycho-behavioral intervention; Part E of supplementary
17 file 1).
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22 **Estimation of costs**

23 The study estimates overall and categorical costs (direct costs only) for each of the RIC
24 procedures (e.g., lung function examination, computed tomography, white blood cell
25 count) identified above using micro-costing techniques.^{29 30} Taking the example of lung
26 function examination, categorical costs include costs on personnel, equipment, materials,
27 regents and others need in completing the examination; while overall cost of the
28 procedure equals the sum of all these categorical costs. In addition, the study also
29 calculates overall cost on individual inpatient by adding up the overall costs on all the
30 clinical procedures he/she has received.
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35 **Measurement of effectiveness**

36 The study uses both proximal variables of outcome (PV) and ultimate outcome (UO)
37 measures of effectiveness of RIC procedures. The UO indicators derive from a follow up
38 survey about 2 years and half after the first hospitalization and include survival,
39 progression-free survival (PFS), quality of life, and quality adjusted life years (QALYs).
40 Here, quality of life is assessed using the widely recognized EQ-5D instrument.³¹
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44 The PV measures come from RIC records and include Eastern Cooperative Oncology
45 Group (ECOG), Karnofsky performance status (KPS) and compiled scores of: a)
46 symptoms (e.g., chronic cough, chest pain, wasting syndrome); b) lung functions (e.g.,
47 forced vital capacity, forced one second expiratory volume), c) image findings (e.g.,
48 number of nodules identified in the lung, size of the largest nodules, presence of pleura
49 or pericardial effusion). Each of these domain specific PV scores equals weighted sum of
50 all sub-indicators within the domain. For example, the compiled score of “lung functions”
51 equals the sum of weighted values of forced vital capacity, forced one second expiratory
52 volume etc. Here the weights come from the coefficients of multivariate regression
53 modeling using an UO indicator (e.g., survival) as the dependent variable; while forced
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vital capacity, forced one second expiratory volume etc. as the independent variables; and stage of disease, age, gender and others as the confounding variables.

Calculation of cost-effectiveness

The study adopts cost-effectiveness ratios (CERs) and relative cost-effectiveness ratio (RCERs) as the main indicators for measuring cost-effectiveness. Here RCER is defined by the difference in cost between two selected sets of RIC procedures, divided by the difference in their effect. More specifically, $RCER = (C_{r+x} - C_r) / (E_{r+x} - E_r)$, where C_r and E_r is the cost and effect in the reference group and C_{r+x} and E_{r+x} , the cost and effect in the group who have underwent all the procedures in the reference group plus x, a specific procedure under concern.³² Suppose, x represents a commonly used traditional Chinese medicine (TCM) which incurs 100 dollars; while r, a typical combination of diagnosis and treatment procedures without the TCM. The combination costs 1000 dollars and the survival time of patients who have adopted this combination is 1.5 years on average; while the same figure for patients who have used the combination plus the TCM is 1.51. Then the $C_{r+x} = 1000 + 100 = 1100$ dollars and the ICER of the TCM = $(1100-1000)/(1.51-1.5)=10000$ dollars.

Identification of influencing factors

The study also extracts, from RIC records, data about patient factors commonly believed to be linked with disease progression, treatment response and outcomes and utilization of RIC procedures. These include: a) socio-demographics (e.g., age, gender, body height and weight, education, employment, marital status, medical insurance); b) risk behaviors and histories (e.g., smoking, alcohol drinking, history of cancer among family members); c) historical and biological test findings (e.g., value of ALK, KRAS, EGFR, PDL1, CEA, CA125, proGRP); d) comorbidities and complications (e.g., presence of superior vena cava syndrome, brain metastases) and stage of disease. Here, disease staging uses TNM system and this staging will be treated as the most important factor throughout the data analysis especially in its effects on the flow of different pathways and their cost-effectiveness.

Selection of participants

The study is implemented in Anhui, an inland province located in middle and east China. It has a population of 61.4 million and its per capita GDP and income rank in the middle (14th) among all provinces in the nation.^{33 34} The social, cultural and economic background of Anhui is representative of over 80% of the whole population in China.^{33 34} The province has 68 rural counties and each of them divides into 10 to 20 townships. Selection of participating counties, townships, patients and RIC case records uses a clustered random sampling which proceeds in 5 steps. Step 1 classifies all the counties in Anhui into southern, northern and middle areas. Step 2 randomly selects 3 counties from each of these areas (12 counties in total). Step 3 randomly draws 4 townships from each of the counties selected (48 townships in total). Step 4 searches the provincial

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3 reimbursement database of the New Rural Cooperative Medical System (NRCMS) and
4 identifies all the patients within the selected townships who had been first diagnosed with
5 primary lung cancer during July 1, 2014 and June 30, 2015. Step 5 searches the database
6 again for all episodes of hospitalization due to the lung cancer for the patients identified
7 in step 4. NRCMS covers 98% of the rural residents and the estimated number of patients
8 and admission episodes is about 5,000 and 25,000 respectively.
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11 The above sample size was determined by our study purpose of building multivariate
12 models of factors affecting the cost-effectiveness of specific routine inpatient care (RIC)
13 pathways. Lung cancer patients generally receive 4 to 6 rounds of inpatient care. Given
14 the various diagnostic and treatment procedures available, there are hundreds of potential
15 RIC pathways (combinations of diagnosis and treatment procedures from the first to the
16 last round of RIC). We plan to group these pathways into manageable (around 20)
17 categories depending on the resultant distribution of the actual pathways and we aim to
18 enter 20-30 factors into the cost-effectiveness model for each of these categorical
19 pathways. Based on these pre-conditions and that the sample size of a multi-variable
20 model should generally be 10 times the number of independent variables, we need 250
21 patients for each pathway. This translates into 5000 patients in total.
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27 **Data collection**

28 The study obtains data through follow-up survey and data extraction. The follow-up
29 survey applies to all the lung cancer patients identified above. It solicits information
30 about the patient's: a) disease progression (i.e., died, alive with or without progression);
31 b) if died, date of death; c) additional admissions due to the lung cancer not included in
32 the above mentioned NRCMS database. The survey uses a short structured questionnaire
33 (supplementary file 2). Administration of the questionnaire starts with a telephone
34 interview (of the patient under concern or his/her close relatives for up to 5 time attempts)
35 followed by a face-to-face interview (of the same respondents for up to 2 attempts) if the
36 telephone contacts failed. The recruitment strives to reach over 85% rate of participation.
37 And the researchers are trained to keep detailed record of reasons they lose some of the
38 patients so as to allow for assessing potential biases. The data extraction applies to
39 records of all the hospital admission episodes identified via the NRCMS database and the
40 follow up survey. It uses a structured form (supplementary file 1) and extracts data about
41 the clinical procedures, costs, effectiveness and influencing factors described above. Two
42 experienced clinicians on care of lung cancer perform the data extraction. They visit (on
43 one-by-one base) all the relevant hospitals, ask for permission to examine the full records
44 and fill the worksheet independently first followed by discussions, if applicable, to solve
45 discrepancies.
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53 **Data analysis**

54 The data collected above allow a variety of descriptive and multivariate analysis
55 centering on the effectiveness, costs and cost-effectiveness of RIC. The effectiveness
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3 analysis comprises all the UO indicators mentioned above including progression free
4 survival, overall survival, quality of life and DALYs. For each of these UO indicators,
5 the analysis will produce: a) estimation of average rates or values with 95% confidence
6 intervals at different time points after first diagnosis by disease stage, PV indicators, RIC
7 pathways, non-hospital care categories, age range etc.; b) multivariate regression models
8 using similar variables as independent variables; and c) path models using as disease
9 stage, RIC pathways, non-hospital care categories, age range etc. as exogenous, complied
10 PV indices as direct endogenous, and individual PV indicators as indirect endogenous
11 variables (Figure 1a). Area under ROC (receiver operating characteristic) curve will be
12 calculated for assessing the predictability of models using binary classifier as the
13 dependent variable (e.g., models of progression free survival, overall survival).
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18 The cost analysis explores mainly: a) overall and categorical costs on different rounds of
19 hospitalization by socio-demographic and selected clinical conditions (Figure 2); b)
20 scatter plot of RIC procedures using the occurrence rate and unit cost of individual
21 procedures as the coordinates; c) multivariate regression models of overall and selected
22 categorical costs using disease stage, PV indicators, RIC pathways, non-hospital care
23 categories, age range etc. as independent variables; and d) Markov models of mean cost
24 for managing lung cancer patients (Figure 1b).
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28 The cost-effectiveness analysis focuses primarily on constructing a pathway tree to help
29 identify the most and the least cost-effective pathways and estimate expected overall and
30 pathway specific cost, effectiveness and cost-effectiveness ratios. The tree consists of
31 different branches of combinations of RIC procedures starting from the first to the last
32 episode of inpatient care labeled with estimated cost, effectiveness and cost-effectiveness
33 ratios (CERs) (Figure 3). Relevance of the pathway tree is tested by means of, for
34 instance, varying the percentage of patient flowing among the different pathways or the
35 cost of major diagnostic and treatment procedures consisting the braches and then
36 examine changes in the ranking of most or least cost-effective pathways. The analysis
37 also pays particular attention to identifying as many as comparable pairs of RIC
38 pathways as possible and calculating RCERs accordingly in a hope to uncover potential
39 pathways with practice, policy and research implications.
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45 The pathway tree construction will use TreeAge³⁵; while the descriptive and multi-
46 variate model analysis, SPSS 16. Cases with missing data about a specific item will be
47 excluded from the analysis involving the item and where applicable, the statistical null
48 hypothesis is be rejected at the significance level of $\alpha = 0.05$.
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51 **Ethics and dissemination**

52 The study involves retrieving RIC records and recruiting patients or their relatives. So it
53 adheres to rigorous human subject protection principles. The study protocol had been
54 reviewed and approved by the Biomedical Ethics Committee of Anhui Medical
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3 University (reference number: 20170312). Participation of hospitals, patients and their
4 relatives are voluntary and written informed consent is required for all participants.
5 Findings from the study will be disseminated through conventional academic routes such
6 as peer-reviewed publications and presentations and regional, national and international
7 conferences.
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10 **Discussion**

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13 The study would share the experience of lung cancer care from the rural Chinese
14 perspective. It is an important sharing of knowledge on population-based lung cancer
15 care, especially since most economic evidence comes from Europe and North America.
16 As mentioned earlier in introduction, China has a unique clinical care system. In China,
17 traditional Chinese medicine is used to complement or replace western medicine. This
18 results in quite different pathways of lung cancer care that have seldom been well
19 explored in published literatures. China has a long history of almost no charges being
20 made for clinical consultations and most patients are used to paying only for medicines,
21 laboratory tests and equipment-based examinations. This forms a perverse financial
22 incentive for clinicians for ordering more sophisticated examinations and tests and for
23 over prescribing. China's lack of referral and follow up mechanisms also merits
24 particular attention. As an individual patient changes from one hospital (say for the first
25 round of treatment) to another (for the second round treatment), he/she may receive
26 different treatment regimens. Discontinued treatment and follow up may make it hard for
27 clinicians to base their treatment decisions on observed effects.
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34 Perhaps the most noteworthy findings of the current study may be the description of the
35 pathways of RIC procedures and their links with cost-effectiveness (Figure 2). These
36 pathways will provide easily understandable means for estimating and identifying,
37 among others, the following: a) which pathways or combinations of procedures happen
38 most or least in routine practice during different rounds of hospitalization for inpatients
39 suffering from lung cancer in rural China; b) which pathways (from the first to last round
40 of hospitalization) incur the highest or lowest direct costs; c) which pathways result in
41 the best or worst patient outcome in terms of different PV and UO measures; d) which
42 pathways are most or least cost-effective in terms of e.g., per unit cost gains in PFS, KPS,
43 symptoms, lung functions, image findings, biological test findings, complications and
44 comorbidities. These have important implications for clinical decision-making as well as
45 policy-making.
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51 Another point worth mentioning in particular refers to the links between the domain
52 specific proximate outcome (PV) indices to key ultimate outcome (UO) indicators (e.g.,
53 survival) generated via a large scale (involving 5000 lung cancer patients) retrospective
54 cohort study. They provide useful references for clinicians on care of lung cancer patients
55 in selecting appropriate procedures to achieve optimal collective contributions to UO.³⁶
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3 At present, although PV indicators are observed routinely, they are presented to
4 clinicians as individual indicators rather than compiled indices. And given the large
5 number of PV indicators involved and the complex relations between RIC procedures
6 and PV indicators and then UO indicators, it is difficult for practicing clinicians to make
7 balanced decisions upon their personal experiences.³⁷
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10 In addition, this study addresses RIC for lung cancer at hospitals in China from a range
11 of meaningful perspectives. The study reinforces the concepts introduced in the landmark
12 studies of Fisher et al and Wennberg et al, which convincingly demonstrated that high
13 quality was not necessarily associated with high cost.³⁸ Describing inpatient lung cancer
14 care in a view that its value is directly proportional to outcomes and inversely
15 proportional to costs helps in guiding quality improvement by either better outcomes
16 and/or lower costs.³⁹ The study calculates and compares the collective cost-effectiveness
17 of different RIC pathways as a whole and thus informs coordinated inpatient care
18 episodes and procedures at different time points and hospitals. The study enables RCERs
19 estimation for specific guideline recommended procedures (GRPs) using various
20 combinations of real and uncontrollable RIC procedures as the reference and thus
21 enhances understanding and application of GRPs established through well-controlled
22 studies in routine practice contexts.
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28 The study also has limitations. The first limit concerns data reliability. Although the
29 majority of data will be extracted from RIC records kept at hospitals, the study uses self-
30 reported data about quality of life and inpatient, outpatient and home care. Self-reports
31 are prone to various biases including recall issues particularly among the elderly, over or
32 under reporting by the respondents for reasons like perceived expectations from the
33 researchers or for fearing of potential worries or distress. These biases may be reduced to
34 a minimum in our study by means of interviewer training, use of chorological recall and
35 probing techniques, and cross-checks of findings from patient interviews, health
36 insurance database and hospital records. More importantly, the study uses EQ-5D in
37 assessing quality of life. It has already been tested with adequate reliability both
38 internationally and in China. Regarding non-hospitalized care, the study asks only simple
39 questions about what kind of care the patients have experienced and when and for how
40 long. These questions are relatively memorable and easily to answer. The second limit
41 relates to selective study content. The study considers only inpatient care; while patients
42 may use various self-treatment and outpatient treatment in addition to inpatient care.^{40 41}
43 And inpatient and non-inpatient treatment may substitute each other to some extent.
44 These may result in under-estimation of the effectiveness of RIC procedures. Fortunately,
45 this under-estimation may be offset to a large extent by treating non-hospital care as
46 confounders and the study data to be collected allow this exercise. Third, the study
47 considers only direct costs rather than full costs taking both direct and indirect costs into
48 consideration. In addition, different hospitals use different equipment, reagents and
49 medicines. Their quality of case records may also vary substantially. These raise
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3 compatibility concerns in pooling data from different hospitals together and performing
4 aggregate analysis. Finally, readers may raise concerns about representativeness of
5 inpatients to the large cancer patients. Hospitalization rates documented from other
6 countries vary greatly;⁴² while similar data from China are scarce. Our estimation, using
7 the dataset of the lasted province-wide Household Health Survey of Anhui, of the
8 proportion of lung cancer patients who had been admitted to hospitals at least once was
9 as high as 89%.⁴³
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12 13 **Competing interests**

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16 The authors declare no competing interests.
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18 **Authors' contributions**

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21 XS and MD contributed equally in conceiving this project, facilitating protocol and
22 instrument development, and drafting this manuscript. RF, ML, PZ and TJ are kore
23 researchers for cost estimation, record extraction, follow up survey and data analysis
24 respectively. DW provided expertise for overall design of the study, and revised and
25 finalized the manuscript. All authors have read and approved the final submission.
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33 lead and supported by Collaboration Center for Cancer Control of Anhui Medical
34 University, Anhui and Luan Center for Diseases Control and Prevention.
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3 Figure 1 Schematic structure of sample multivariate models to be built
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5 Figure 2 Simulated cost by selected socio-demographics and clinical characteristics
6 (TC=total cost; KRMB=1000 Chinese yuan)
7

8 Figure 3 Anticipated “procedure-outcome” tree of inpatient lung cancer care (Tx = the
9 xth round of hospitalization; Cx = the xth combination of clinical procedures; Px =
10 possibility of using the xth combinations of clinical procedures; Ox = the xth patient
11 outcome index/indicator)
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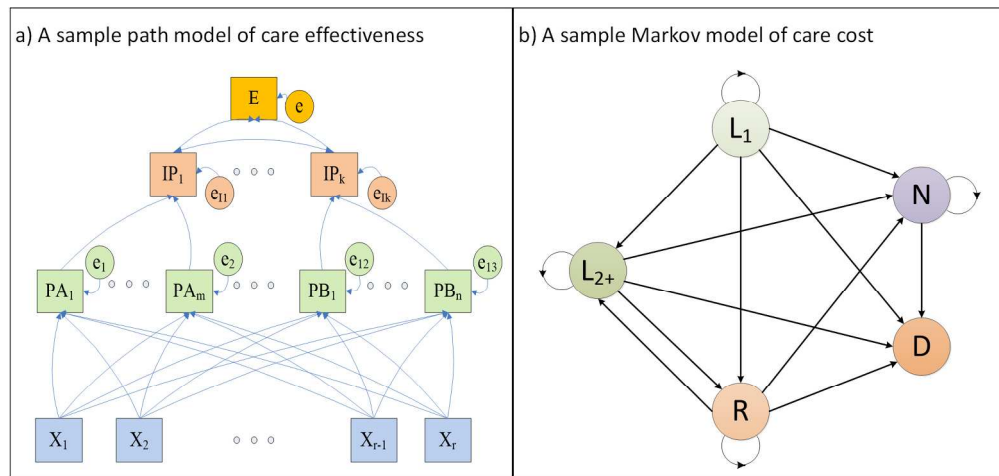


Figure 1 Schematic structure of sample multivariate models to be built/ X=independent variables; PA or PB=domain A or proximate indicators of effectiveness; IP=index of proximate variables; e=systematic error; and E= effectiveness, e.g., overall survival, QALYs; L₁=first line treatment; L₂₊=second or third line treatment; R=remission; N=no active treatment; D=death.

188x88mm (300 x 300 DPI)

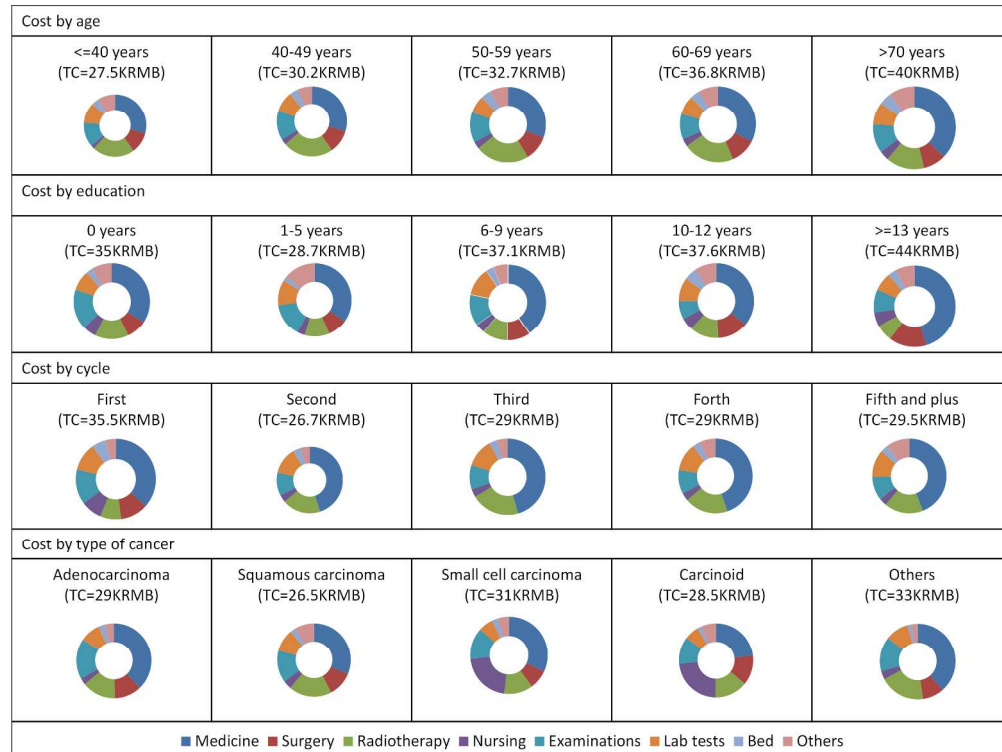


Figure 2 Simulated cost by selected socio-demographics and clinical characteristics (TC=total cost; KRMB=1000 Chinese yuan)

249x187mm (300 x 300 DPI)

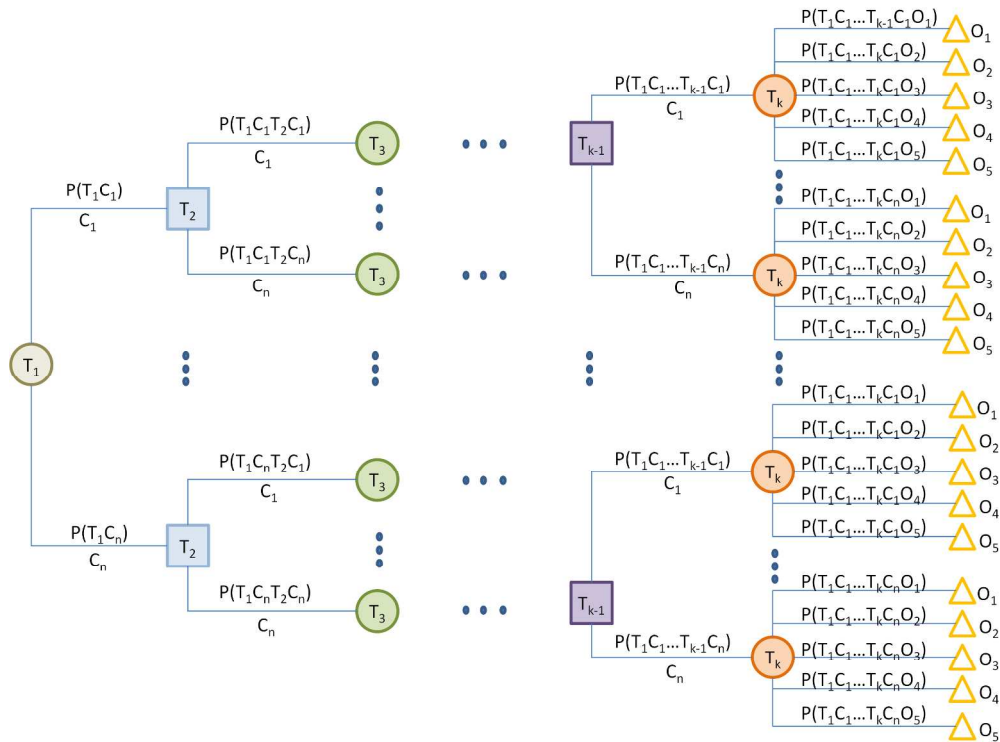


Figure 3 Anticipated "procedure-outcome" tree of inpatient lung cancer care (T_x = the x^{th} round of hospitalization; C_x = the x^{th} combination of clinical procedures; P_x = possibility of using the x^{th} combinations of clinical procedures; O_x = the x^{th} patient outcome index/indicator)

242x183mm (300 x 300 DPI)

Annex 1 Lung cancer inpatient care data extraction form

Reference Number: |_|_|-|_|_|_|_|_|_|_|_|

Part A: Patient's social demographics

1.1 Case record number: |_|_|_|_|_|_|_|_|_|_|

1.2 Patient identification number: |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

1.3 Sex: [1]Male [2]Female

1.4 Birth date (dd-mm-yyyy, first case record only): |_|_|-|_|_|-|_|_|_|_|_|

1.5 Body height (centimeter, first case record only): |_|_|_|_|

1.6 Body weight (kilogram): |_|_|_|_|.|_|

1.7 Education (first case record only):

- | | | |
|-------------------------|--------------------|------------------------|
| [1] No formal education | [2] Primary school | [3] Middle school |
| [4] High school | [5] College | [6] Graduate or higher |
| [7] Not clear | | |

1.8 Occupation (first case record only):

- | | | |
|------------------------------|-----------------------|-------------------|
| [1] Staff of public entities | [2] Employee of firms | [3] Self-employed |
| [4] Peasant | [5] Un-employed | [6] Retired |
| [7] Army member | [8] Not clear | |

1.9 Marital status:

- | | | |
|---------------|-------------|---------------|
| [1] Unmarried | [2] Married | [3] Divorced |
| [4] Widowed | [5] Other | [6] Not clear |

1.10 Medical insurance:

- [1] Essential medical insurance for urban employees
- [2] Medical insurance for urban citizens
- [3] New rural cooperative medical care systems
- [4] Commercial medical insurance
- [5] Public medical care system
- [6] Out-of-pocket care
- [7] Other
- [8] Not clear

Part B: Patient's behavior and disease history (first case record only)

2.1 Smoking:

- | | | |
|--------------------|-----------------------------|----------------|
| [1] Current smoker | [2] Former smoker | [3] Non-smoker |
| [4] Smoker | [9] Not clear (skip to 2.2) | |

2.1.1 Number of cigarettes smoked per day: |_|_|_|_|

2.1.2 Number of years smoked: |_|_|

2.1.3 Number of years ceased smoking: |_|_|

2.2 Previous diagnosis of the following respiratory diseases:

- | | | |
|--------------------|------------------------------|---------------|
| [1] Tuberculosis | [2] Chronic bronchitis | [3] Emphysema |
| [4] Asthma | [5] Silicosis/pneumoconiosis | |
| [6] Other(specify) | | |

2.3 Previous diagnosis of the following cardio-cerebrovascular/endocrine diseases:

- | | | |
|-------------------------|----------------------------|-------------------------|
| [1] Hypertension | [2] Coronary heart disease | [3] Cerebral thrombosis |
| [4] Cerebral hemorrhage | [5] Hyperlipemia | [6] Diabetes |
| [7] Other(specify) | | |

2.4 Previous diagnosis of cancer (enter location of cancer, if applicable, e.g., breast cancer, colorectal cancer)

- | | | |
|-----|-----|-----|
| [1] | [2] | [3] |
| [4] | [5] | [6] |
| [7] | [8] | [9] |

(Please add more cells as needed)

2.5 Previous diagnosis of cancer among relatives

- | Number | Type of relatives | Location of cancer |
|--------|-------------------|--------------------|
| [1] | | |
| [2] | | |
| [3] | | |

(Please add more rows as needed)

Part C: Patient's current symptoms/signs

3.1 Respiratory symptoms/signs

- | | | |
|----------------------|-------------------------|-------------------------|
| [1] Chronic coughing | [2] Sputum with blood | [3] Chest suppression |
| [4] Chest pain | [5] Difficult breathing | [6] Repeated bronchitis |
| [7] Hoarseness | [8] Other (specify) | |
| [9] None | | |

3.2 Symptoms/signs of metabolism or immunity dysfunction:

- | | | |
|---------------------|------------------------------|-----------------|
| [1] None | [2] Hippocratic fingers/toes | [3] Amyasthenia |
| [4] Hyponatremia | [5] Blacken skin folds | |
| [6] Other (specify) | | |

3.3 Symptoms/signs relating to lung cancer metastasis:

- | | | |
|---------------------|-----------------------|---------------------|
| [1] None | [2] Topical pain | [3] Headache |
| [4] Dizzy | [5] Sudden dyskinesia | [6] Facial swelling |
| [7] Other (specify) | | |

3.4 Cancer-related non-specific symptoms/signs:

- | | | |
|-------------------------|-------------------------|--------------|
| [1] None | [2] Apparent emaciation | [3] Weakness |
| [4] Mild/moderate fever | [5] Other (specify) | |

3.5 Karnofsky score:

- | |
|-------------------|
| [1] _ _ _ _ |
| [2] Not available |

3.6 Body surface examination findings:

- | |
|----------|
| [1] None |
|----------|

- 1
2
3 [1] No abnormalities [2] Neck /supraclavicular lymph nodes
4 [3] Others (specify)
5
6

7 4a.8 Chest ultrasonography

- 8 [1] Not performed (skip to 4a.9)
9 [2] Performed

10 4a.8.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

11 4a.8.2 Diagnosis from chest ultrasonography

- 12 [1] No abnormalities [2] Pleural effusion [3] Pericardial effusion
13 [4] Others (specify)
14

15 4a.9 Abdominal ultrasonography

- 16 [1] Not performed (skip to 4a.10)
17 [2] Performed

18 4a.9.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

19 4a.9.2 Diagnosis from abdominal ultrasonography

- 20 [1] No abnormalities [2] Liver metastases [3] Adrenal gland transfer
21 [4] Peritoneal/retroperitoneal lymphadenopathy
22 [5] Others (specify)
23

24 4a.10 Bone scans

- 25 [1] Not performed (skip to 4a.11)
26 [2] Performed

27 4a.10.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

28 4a.10.2 Diagnosis from bone scans

- 29 [1] No abnormalities [2] confirmed metastases [3] Suspected metastases
30 [4] Others (specify)
31

32 4a.10.2.1 If [2] or [3], location of metastases

33 4a.11 PET-CT examination

- 34 [1] Not performed (skip to 4b.1)
35 [2] Performed

36 4a.11.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

37 4a.11.2 Diagnosis from PET-CT examination

- 38 [1] No abnormalities [2] Lung nodules/mass(Primary lesion)
39 [3] Pulmonary metastasis [4] Lymph node metastasis
40 [5] Adrenal gland transfer [6] Bone transfer
41 [7] Other site transfer [8] Thoracic / pericardial effusion
42 [9] Others (specify)
43

44 4a.11.3.1 If [2], location of lung nodules/mass

45 4a.11.3.1.1 Size of the largest nodules/mass: |_|_|.|_|*|_|_|.|_|cm

46 4a.11.3.1.2 SUV

47 4a.11.3.1.3 Nature of the nodules/mass identified:

- 48 [1] Affirmative benign [2] Suspected benign [3] Suspected malignant
49 [4] Affirmative malignant [5] Not clear [6] Others (specify)
50

51 4a.11.3.2 If [3], location of pulmonary metastasis

52 4a.11.3.2.1 SUV
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- 1
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3 4a.11.3.3 If [4], location of lymph node metastasis
4 4a.11.3.3.1SUV
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6 4a.11.3.4 If [5], location of adrenal gland metastasis
7 4a.11.3.4.1SUV
8
9 4a.11.3.5 If [6], location of bone metastases
10 4a.11.3.5.1 SUV
11 4a.11.3.6 If [7], location of other metastases
12 4a.11.3.6.1 SUV
13
14

15 **b) Endoscopic examinations**

16 4b.1 Fiberoptic bronchoscopy

17 [1] Not performed (skip to 4b.2)

18 [2] Performed

19 4b.1.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

20 4b.1.2 Diagnosis from fiberoptic bronchoscopy

21 [1] No abnormalities [2] Tumor

22 [3] Others (specify)

23 [4] Not clear

24 4b.2 Lavage cytology/brushing

25 [1] Not performed (skip to 4b.3)

26 [2] Not clear (skip to 4b.3)

27 [3] Performed

28 4b.2.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

29 4b.3 Bronchoscopy clamp biopsy

30 [1] Not performed (skip to 4b.4)

31 [2] Not clear (skip to 4b.4)

32 [3] Performed

33 4b.3.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

34 4b.4 Bronchoscopy aspiration biopsy

35 [1] Not performed (skip to 4c.0)

36 [2] Not clear (skip to 4c.0)

37 [3] Performed

38 4b.4.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

39 4b.4.2 Type of bronchoscopy aspiration biopsy

40 [1] Endobroncheal ultrasonography [2] Electromagnetic-guided

41 [3] Transbronchial needle aspiration [4] Not clear

42 [5] Others (specify)

c) Laboratory/biological tests

4c.0 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.1 CEA

[1] Not performed (skip to 4c.2)

[2] Not clear (skip to 4c.2)

[3] Performed

4c.1.1 Date of performance if different from 4c.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.1.2 Test result (value-unit): _____ - _____

4c.2 CA125

[1] Not performed (skip to 4c.3)

[2] Not clear (skip to 4c.3)

[3] Performed

4c.2.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.2.2 Test result (value-unit): _____ - _____

4c.3 proGRP

[1] Not performed (skip to 4c.4)

[2] Not clear (skip to 4c.4)

[3] Performed

4c.3.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.3.2 Test result (value-unit): _____ - _____

4c.4 SCC

[1] Not performed (skip to 4c.5)

[2] Not clear (skip to 4c.5)

[3] Performed

4c.4.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.4.2 Test result (value-unit): _____ - _____

4c.5 NSE

[1] Not performed (skip to 4c.6)

[2] Not clear (skip to 4c.6)

[3] Performed

4c.5.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.5.2 Test result (value-unit): _____ - _____

4c.6 CYFRA21-1

[1] Not performed (skip to 4c.7)

[2] Not clear (skip to 4c.7)

[3] Performed

4c.6.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.6.2 Test result (value-unit): _____ - _____

4c.7 WBC

[1] Not performed (skip to 4c.8)

[2] Not clear (skip to 4c.8)

[3] Performed

4c.7.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.7.2 Test result (value-unit): _____ - _____

4c.8 PLT

[1] Not performed (skip to 4c.9)

[2] Not clear (skip to 4c.9)

[3] Performed

4c.8.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.8.2 Test result (value-unit): _____ - _____

4c.9 Hb

[1] Not performed (skip to 4c.10)

[2] Not clear (skip to 4c.10)

[3] Performed

4c.9.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.9.2 Test result (value-unit): _____ - _____

4c.10 ALB

[1] Not performed (skip to 4c.11)

[2] Not clear (skip to 4c.11)

[3] Performed

4c.10.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.10.2 Test result (value-unit): _____ - _____

4c.11 Pre-ALB

[1] Not performed (skip to 4c.12)

[2] Not clear (skip to 4c.12)

[3] Performed

4c.11.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.11.2 Test result (value-unit): _____ - _____

4c.12 Ca

[1] Not performed (skip to 4c.13)

[2] Not clear (skip to 4c.13)

[3] Performed

4c.12.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.12.2 Test result (value-unit): _____ - _____

4c.13 Fe

[1] Not performed (skip to 4c.14)

[2] Not clear (skip to 4c.14)

[3] Performed

4c.13.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.13.2 Test result (value-unit): _____ - _____

4c.14 FIB

[1] Not performed (skip to 4c.15)

[2] Not clear (skip to 4c.15)

[3] Performed

4c.14.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.14.2 Test result (value-unit): _____ - _____

4c.15 D-D

[1] Not performed (skip to 4c.16)

[2] Not clear (skip to 4c.16)

[3] Performed

4c.15.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.15.2 Test result (value-unit): _____ - _____

4c.16 Na

[1] Not performed (skip to 4c.17)

[2] Not clear (skip to 4c.17)

[3] Performed

4c.16.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.16.2 Test result (value-unit): _____ - _____

4c.17 LDL

[1] Not performed (skip to 4c.18)

[2] Not clear (skip to 4c.18)

[3] Performed

4c.17.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.17.2 Test result (value-unit): _____ - _____

4c.18 LDL

[1] Not performed (skip to 4c.19)

[2] Not clear (skip to 4c.19)

[3] Performed

4c.18.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.18.2 Test result (value-unit): _____ - _____

4c.19 TG

[1] Not performed (skip to 4c.20)

[2] Not clear (skip to 4c.20)

[3] Performed

4c.19.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.19.2 Test result (value-unit): _____ - _____

4c.20 TCHOL

[1] Not performed (skip to 4d.1)

[2] Not clear (skip to 4d.1)

[3] Performed

4c.20.1 Date of performance if different from 6.0

(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4c.20.2 Test result (value-unit): _____ - _____

d) Heart and lung function examinations

4d.1 Electrocardiogram examination

[1] Not performed (skip to 4d.2)

[2] Performed

4d.1.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4d.1.2 Heart rate: |_|_|_| times/minutes

4d.1.3 Diagnosis from electrocardiogram examination

[1] No abnormalities

[2] Abnormalities(specify)

4d.2 Lung function examinations

[1] Not performed (skip to 4e.1)

[2] Not clear (skip to 4e.1)

[3] Performed

4d.2.1 Date of performance (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

4d.2.2 FVC (Tested/predicted value): /

4d.2.3 FEV1(Tested/predicted value): /

4d.2.4 FEV1/FVC%(Tested/predicted value): /

4d.2.5 TLCO SB(Tested/predicted value): /

4d.2.6 Ventilation function assessment:

[1] No abnormalities [2] Mildly reduced [3] Moderately reduced

[4] Severely reduced [5] Restrictive [6] Obstruction

[7] Mixed [8] Not clear

4d.2.7 Lung capacity

[1] No abnormalities [2] Increased total residue ratio [3] Low lung capacity

[4] Not clear

4d.2.8 Breath diffusion

[1] No abnormalities [2] Reduced [3] Not clear

e) Histological/cytological examination

4e.1 Preoperative cytological

[1] Not performed (skip to 4e.2)

[2] Not clear (skip to 4e.2)

[3] Performed

4e.1.1 If [3], preoperative cytological method:

[1] Needle biopsy [2] Sputum specimen examination [3] Bronchial lavage

[4] Others (specify)

4e.1.2 If [3], preoperative cytological result:

[1] With cancer cells [2] Without cancer cells [3] Uncertain lesion

[4] Not clear

4e.1.2.1 If '4e.1.2' selected [1], cytological type

[1] Adenocarcinoma [2] Squamous cell carcinoma

[3] Small cell carcinoma [4] Carcinoid

[5] Large cell carcinoma [6] Squamous cell carcinoma

[7] Sarcomatoid carcinoma [8] carcinoma from sialaden

[9] Not clear [10] Others (specify)

4e.1.2.1.1 If '4e.1.2.1' selected [1], first class subtype code

[1] Pre-invasion lesion [2] Microinvasive adenocarcinoma

[3] Invasive adenocarcinoma [4] Variant invasive adenocarcinoma

[5] Others (specify)

[6] Not clear

4e.1.2.1.1.1 If '4e.1.2.1.1' selected [1], second class subtype code

[1] Atypical adenocarcinoma like hyperplasia

[2] Adenocarcinoma in situ

[3] Not clear

4e.1.2.1.1.2 If '4e.1.2.1.1' selected [3], second class subtype code

[1] Accumbens dominated [2] Acinar dominated

[3] Papillary dominated [4] Micro papillae dominated

[5] Entities with mucus dominated

[6] Not clear

4e.1.2.1.1.3 If '4e.1.2.1.1' selected [4], second class subtype code

[1] Mucinous invasive adenocarcinoma

[2] Colloid [3] Fetal

[4] Intestinal [5] Others (specify)

[6] Not clear

4e.2 Preoperative histological

[1] Not performed (skip to 4e.3)

[2] Not clear (skip to 4e.3)

[3] Performed

4e.2.1 If [3], method of preoperative histological biopsy:

[1] Ultrasound guided aspiration biopsy [2] CT guided aspiration biopsy

- 1
2
3 [3] Bronchoscopic biopsy [4] Nuclear magnetic puncture
4 [5] Not clear [6] Others (specify)
5
6 4e.2.2 If [3], results of preoperative histological biopsy:
7 [1] With cancer cells [2] Without cancer cells [3] Uncertain lesion
8 [4] Not clear
9
10 4e.2.2.1 If [1], histological type:
11 [1] Adenocarcinoma [2] Squamous cell carcinoma
12 [3] Small cell carcinoma [4] Carcinoid
13 [5] Large cell carcinoma [6] Squamous cell carcinoma
14 [7] Sarcomatoid carcinoma [8] carcinoma from sialaden
15 [9] Not clear [10] Others (specify)
16
17 4e.2.2.1.1 If '4e.2.2.1' selected [1], first class subtype code
18 [1] Pre-invasion lesion [2] Microinvasive adenocarcinoma
19 [3] Invasive adenocarcinoma [4] Variant invasive adenocarcinoma
20 [5] Others (specify)
21 [6] Not clear
22
23 4e.2.2.1.1 If '4e.2.2.1.1' selected [1], second class subtype code
24 [1] Atypical adenocarcinoma like hyperplasia
25 [2] Adenocarcinoma in situ
26 [3] Not clear
27
28 4e.2.2.1.1.2 If '4e.2.2.1.1' selected [3], second class subtype code
29 [1] Accumbens dominated [2] Acinar dominated
30 [3] Papillary dominated [4] Micro papillae dominated
31 [5] Entities with mucus dominated
32 [6] Not clear
33
34 4e.2.2.1.1.3 If '4e.2.2.1.1' selected [4], second class subtype code
35 [1] Mucinous invasive adenocarcinoma
36 [2] Colloid [3] Fetal
37 [4] Intestinal [5] Others (specify)
38 [6] Not clear
39
40 4e.2.2.2 If 4e.2.2.1 information not available, please tick in histology type:
41 [1] Small cell lung cancer [2] Non-small cell lung cancer [3] Benign lesion
42 [4] Not clear [5] Others (specify)
43
44
45
46
47 4e.3 Intraoperative biopsy of frozen mass:
48 [1] Not performed (skip to 4e.4)
49 [2] Not clear (skip to 4e.4)
50 [3] Performed
51
52 4e.3.1 If [3], diagnosis of frozen mass biopsy:
53 [1] Adenocarcinoma [2] Squamous cell carcinoma
54 [3] Small cell carcinoma [4] Carcinoid
55 [5] Large cell carcinoma [6] Squamous cell carcinoma
56 [7] Sarcomatoid carcinoma [8] carcinoma from sialaden
57 [9] Not clear [10] Others (specify)
58
59 4e.3.1.1 If '4e.3.1' selected [1], first class subtype code
60

- 1
2
3 [1] Pre-invasion lesion [2] Micro invasive adenocarcinoma
4 [3] Invasive adenocarcinoma [4] Variant invasive adenocarcinoma
5 [5] Others (specify)
6 [6] Not clear
7
8 4e.3.1.1.1 If '4e.3.1.1' selected [1], second class subtype code
9
10 [1] Atypical adenocarcinoma like hyperplasia
11 [2] Adenocarcinoma in situ
12 [3] Not clear
13 4e.3.1.1.2 If '4e.3.1.1' selected [3], second class subtype code
14
15 [1] Accumbens dominated [2] Acinar dominated
16 [3] Papillary dominated [4] Micro papillae dominated
17 [5] Entities with mucus dominated
18 [6] Not clear
19 4e.3.1.1.3 If '4e.3.1.1' selected [4], second class subtype code
20
21 [1] Mucinous invasive adenocarcinoma
22 [2] Colloid [3] Fetal
23 [4] Intestinal [5] Others (specify)
24 [6] Not clear
25
26

27 4e.4 Intraoperative biopsy of lymph node:

- 28 [1] Not performed (skip to 4e.5)
29 [2] Not clear (skip to 4e.5)
30 [3] Performed
31
32 4e.4.1 If [3], result of lymph node biopsy:
33 [1] Metastasis [2] No metastasis
34
35

36 4e.5 Intraoperative biopsy of frozen margin of bronchus:

- 37 [1] Not performed (skip to 4e.6)
38 [2] Not clear (skip to 4e.6)
39 [3] Performed
40
41 4e.5.1 If [3], result of frozen margin of bronchus:
42 [1] Margin tumor [2] No margin tumor
43
44

45 4e.6 Postoperative histological

- 46 [1] Not performed (skip to 4e.7.1)
47 [2] Not clear (skip to 4e.7.1)
48 [3] Performed
49 4e.6.1 If [3], number of tumors:
50 [1] Solitary tumor [2] More than 2 nodules [3] Not clear
51 4e.6.1.1 The largest tumor size: |_|_|*|_|_|*|_|_|cm
52 4e.6.1.2 If multiple tumor, the smallest tumor size: |_|_|*|_|_|*|_|_|cm
53
54 4e.6.2 Pathologic diagnosis
55
56 [1] Adenocarcinoma [2] Squamous cell carcinoma
57 [3] Small cell carcinoma [4] Carcinoid
58 [5] Large cell carcinoma [6] Squamous cell carcinoma
59 [7] Sarcomatoid carcinoma [8] carcinoma from sialaden
60

- 1
2
3 [9] Not clear [10] Others (specify)
4 4e.6.2.1 If '4e.6.2' selected [1], first class subtype code
5 [1] Pre-invasion lesion [2] Micro invasive adenocarcinoma
6 [3] Invasive adenocarcinoma [4] Variant invasive adenocarcinoma
7 [5] Others (specify)
8 [6] Not clear
9
10 4e.6.2.1.1 If '4e.6.2.1' selected [1], second class subtype code
11 [1] Atypical adenocarcinoma like hyperplasia
12 [2] Adenocarcinoma in situ
13 [6] Not clear
14
15 4e.6.2.1.2 If '4e.6.2.1' selected [3], second class subtype code
16 [1] Accumbens dominated [2] Acinar dominated
17 [3] Papillary dominated [4] Micro papillae dominated
18 [5] Entities with mucus dominated
19 [6] Not clear
20
21 4e.6.2.1.3 If '4e.6.2.1' selected [4], second class subtype code
22 [1] Mucinous invasive adenocarcinoma
23 [2] Colloid [3] Fetal
24 [4] Intestinal [5] Others (specify)
25 [6] Not clear
26
27 4e.6.3 Differentiation degree:
28 [1] Well differentiated [2] Well and moderately differentiated
29 [3] Moderately differentiated [4] Poorly differentiated
30 [5] Middle and low differentiation [6] Undifferentiated
31 [7] Not clear
32
33 4e.6.4 Associated with intrapulmonary metastasis
34 [1] Yes [2] No (skip to 4e.6.9) [3] Not clear(skip to 4e.6.9)
35
36 4e.6.5 Invasion of pleura?
37 [1] Yes [2] No [3] Not clear
38
39 4e.6.6 Invasion of the main bronchi?
40 [1] Yes, distance is less than 2cm [2] Yes, distance is more than 2cm
41 [3] No [3] Not clear
42
43 4e.6.7 Invasion of chest wall/septum/mediastinum/pericardium?
44 [1] Yes(specify) [2] No [3] Not clear
45
46 4e.6.8 Invasion of mediastinum/heart/trachea/esophagus/vertebral body/carina?
47 [1] Yes(specify) [2] No [3] Not clear
48
49 4e.6.9 Resection margin positive?
50 [1] Not performed (skip to 4e.6.10)
51 [2] Not clear (skip to 4e.6.10)
52 [3] Positive
53 [4] Negative
54
55 4e.6.10 The total number of lymph nodes detected
56
57 4e.6.11 The total number of lymph node metastasis
58
59 4e.6.12 Lymph node metastasis site
60

- 1
2
3 [1] No metastasis [2] Ipsilateral bronchi or hilum
4 [3] Ipsilateral mediastinum or carina
5 [4] Contralateral mediastinum or hilum of lung, clavicle
6 [5] Not clear
7
8

9 4e.7 Tumor marker

10 4e.7.1 Her-2(C-erbB-2) detection

11 [1] Not performed (skip to 4e.7.2)

12 [2] Not clear (skip to 4e.7.2)

13 [3] Performed (skip to 4e.7.2)

14 4e.7.1.1 If [3], method of detection

15 [1] Immunohistochemistry [2] FISH [3] Other(Specify)

16 4e.7.1.2 If [3], result of detection

17 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear

18 4e.7.2 Anaplastic lymphoma kinase(ALK) detection

19 [1] Not performed (skip to 4e.7.3)

20 [2] Not clear (skip to 4e.7.3)

21 [3] Performed (skip to 4e.7.3)

22 4e.7.2.1 If [3], method of detection

23 [1] Immunohistochemistry [2] Genetic testing [3] Other(Specify)

24 4e.7.2.2 If [3], result of detection

25 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear

26 4e.7.3 Epidermal growth factor receptor(EGFR) detection

27 [1] Not performed (skip to 4e.7.4)

28 [2] Not clear (skip to 4e.7.4)

29 [3] Performed (skip to 4e.7.4)

30 4e.7.4.1 If [3], method of detection

31 [1] Immunohistochemistry [2] Genetic testing [3] Other(Specify)

32 4e.7.3.2 If [3], result of detection

33 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear

34 4e.7.4 K-ras detection

35 [1] Not performed (skip to 4e.7.5)

36 [2] Not clear (skip to 4e.7.5)

37 [3] Performed (skip to 4e.7.5)

38 4e.7.4.1 If [3], method of detection

39 [1] Immunohistochemistry [2] Gene mutation detection [3] Other(Specify)

40 4e.7.4.2 If [3], result of detection

41 [1] Positive [2] Negative [3] Other(Specify) [4] Not clear

42 4e.7.5 Other gene factor types detection

43 [1] Not performed (skip to 4f.1)

44 [2] Not clear (skip to 4f.1)

45 [3] Performed (skip to 4f.1)

46 4e.7.6.1 If [3], method of detection

47 [1] Immunohistochemistry [2] Gene mutation detection [3] Other(Specify)

48 4e.7.6.2 If [3], result of detection

[1] Positive [2] Negative [3] Other(Specify) [4] Not clear

f) Staging of lung cancer

4f.1 Type of staging available

[1] Clinical stage [2] Pathological staging [3] Not staging
[4] Not clear

4f.2 Staging methods

[1] Clinical imaging [2] Pathological staging [3] Postoperative pathology
[4] No [5] Not clear

4f.3 If staged, details of TNM staging

4f.3.1 Staging system

[1] The 6th edition of UICC/AJCC staging, published in 2002
[2] The 7th edition of AHCC staging, published in 2009

4f.3.2 T staging

[1] T1; [2] T2; [3] T3; [4] T4; [5] Tx; [6] Not clear

4f.3.3 N staging

[1] N1; [2] N2; [3] N3; [4] N0; [5] Not clear

4f.3.4 M staging

[1] M1; [2] Mx; [3] M0; [4] Not clear

4f.3.5 TNM staging

[1] Stage I; [2] Stage IIA; [3] Stage IIB; [4] Stage IIIA;
[5] Stage IIIB; [6] Stage IV; [7] Others (specify); [8] Not clear

4f.4 Type of lung cancer:

[1] Small cell lung cancer [2] Non-Small cell lung cancer
[3] Mixed small cell lung cancer [4] Not clear
[5] Others (specify)

4f.4.1 If [1], state of lesion

[1] Restricted [2] Pervasive
[3] Other (specify)

4f.4.2 If [2], state of lesion

[1] Early stage [2] Locally advanced
[3] Advanced [4] Not clear

Part E: Treatment procedures and findings/results

5.1 Surgical treatment

[1] Not performed (skip to 5.2)
[2] Thoracotomy
[3] Video-assisted thoracoscopic surgery
[4] Thoracoscope assisted small incision surgery
[5] Others (specify)
[6] Not clear(skip to 5.2)

5.1.1 Details of resection:

- | | |
|------------------------|--|
| [1] Lobectomy | [2] Segmental resection |
| [3] Combined lobectomy | [4] Completely pneumonectomy |
| [5] Sleeve lobectomy | [6] Resection and reconstruction of carina |
| [7] Others (specify) | [8] Not clear |

5.1.1.1 If [2], name of the segment

5.1.1.2 If [4], treatment of pulmonary arteriovenous in pericardium

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.2 If [3], type of thoracoscope assistance:

- | | | |
|--------------------|------------------|-----------------|
| [1] Single hole | [2] Double holes | [3] Three holes |
| [4] Multiple holes | [5] Not clear | |

5.1.2.1 Conversion from video-assisted thoracoscopic surgery to Thoracotomy

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.3 Performance of rapid pathology

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.4 Findings from intraoperative exploration

5.1.4.1 Tumor site

- | | | |
|------------------|------------------|-----------------|
| [1] Left | [2] Right | [3] Upper lobes |
| [4] Bottom lobes | [5] Middle lobes | [6] Not clear |

5.1.4.2 Cross lobes

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.4.3 Pleural involvement/ Shrinkage

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.4.4 Largest diameter of tumor: |||cm

5.1.4.5 Pleural metastasis

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.4.6 Intrapulmonary metastasis

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.4.7 Foreign invasion

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.4.7.1 If [1], name of invaded tissue:

5.1.4.8 Dual(Multiple) primary tumor

- | | | |
|---------|--------|---------------|
| [1] Yes | [2] No | [3] Not clear |
|---------|--------|---------------|

5.1.5 Lymph node dissection

- | | | | |
|--------------------|--------------|-----------------|---------------|
| [1] Systematicness | [2] Sampling | [3] Not cleaned | [4] Not Clear |
|--------------------|--------------|-----------------|---------------|

5.1.6 Classification of surgery

- | | | |
|------------------|--------------------------|---------------|
| [1] Radical cure | [2] Palliative treatment | [3] Not clear |
|------------------|--------------------------|---------------|

5.2 Radiation therapy

[1] Not performed (skip to 5.3)

[2] Not clear (skip to 5.3)

[3] Performed

5.2.1 If [3], type of radiation therapy:

[1] Preoperative radiotherapy [2] Postoperative radiotherapy

[3] Radical radiation therapy

1
2
3 5.2.1.1 Combined with chemotherapy:

4 [1] Not performed (skip to 10.1.3)

5 [2] Not clear (skip to 10.1.3)

6 [3] Performed

7 5.2.1.1.1 If [3], type of chemo-radiotherapy:

8 [1] Sequence chemoradiotherapy [2] Concurrent chemoradiotherapy

9 5.2.1.1.2 If [2], name of the chemotherapy drugs

10 5.2.1.1.3 If [2], chemotherapy cycles:

11 [1] Every week [2] Biweekly [3] Every 3 weeks

12 [4] Every 4 weeks [5] Not clear

13 5.2.1.2 Radiotherapy technique

14 [1] Routine radiotherapy [2] Three-dimensional conformal radiotherapy

15 [3] Tomo treatment [4] Static intensity modulated radiotherapy

16 [5] Stereotactic radiotherapy [6] Rotational intensity modulated radiotherapy

17 [7] Not clear [8] Others (specify)

18 5.2.1.3 Polarization

19 [1] Conventional simulator [2] CT simulation [3] 4D-CT

20 [4] Not clear

21 5.2.1.4 Methods of pretreatment position verification

22 [1] No methods [2] Image guide radiation therapy

23 [3] Not clear [4] Electronic Portal Imaging Device

24 [5] Others (specify)

25 5.2.1.5 Radiation target area (multiple choice)

26 [1] Primary foci [2] Postoperative stump and tumor bed

27 [3] Involving lymph node irradiation [4] Choose lymph node irradiation

28 [5] Metastatic lesions [6] Not clear

29 5.2.1.6 Radiotherapy dose division program

30 No Radiation energy Total dose Gy Number of times Treatment time (days)

31 [1]

32 [2]

33 [3]

34 5.3 Chemotherapy

35 [1] Not performed (skip to 5.4)

36 [2] Not clear (skip to 5.4)

37 [3] Performed

38 5.3.1 If [3], type of chemotherapy:

39 [1] Neoadjuvant chemotherapy [2] Postoperative adjuvant chemotherapy

40 [3] Advanced chemotherapy [4] Others (specify)

41 5.3.1.1 If [1], neoadjuvant chemotherapy regimen

42 [1] Vinorelbine/Cisplatin+Vinorelbine/Carboplatin+Vinorelbine/Other platinum

43 [2] Paclitaxel/Cisplatin+Paclitaxel/Carboplatin+Paclitaxel/Other platinum

44 [3] Docetaxel/Cisplatin+ Docetaxel/Carboplatin +Docetaxel/Other platinum

45 [4] Pemetrexed/Cisplatin+Pemetrexed/Carboplatin+ Pemetrexed/Other platinum

46 [5] Gemcitabine/Cisplatin +Gemcitabine/Carboplatin +Gemcitabine/Other platinum

[6] Others (specify)

[7] Not clear

5.3.1.2 If [2], postoperative adjuvant chemotherapy regimen:

[1] Vinorelbine/Cisplatin+Vinorelbine/Carboplatin+Vinorelbine/Other platinum

[2] Paclitaxel/Cisplatin+Paclitaxel/Carboplatin+Paclitaxel/Other platinum

[3] Docetaxel/Cisplatin+Docetaxel/Carboplatin+Docetaxel/Other platinum

[4] Pemetrexed/Cisplatin+Pemetrexed/Carboplatin+Pemetrexed/Other platinum

[5] Gemcitabine/Cisplatin+Gemcitabine/Carboplatin+Gemcitabine/Other platinum

[6] Etoposide/Cisplatin+Etoposide/Carboplatin+Cyclophosphamide/Adriamycin/
Vincristine

[7] Others (specify)

[8] Not clear

5.3.1.3 If [3], advanced chemotherapy regimen:

[1] Cisplatin+Carboplatin+Other platinum

[2] Paclitaxel+Docetaxel

[3] Emetabine

[4] Pemetrexed

[5] Vinorelbine+Vincristine

[6] Irinotecan+Topotecan

[7] Tegafur

[8] Etoposide

[9] Cytosine+Ifosfamide

[10] Adriamycin

[11] Others(specify)

[12] Not clear

5.4 Complication/comorbidities treatment

5.4.1 Superior vena cava syndrome

[1] Not appeared(skip to 5.4.2) [2] Not clear(skip to 5.4.2) [3] Appeared

5.4.1.1 If [3], duration (month):

5.4.1.2 If [3], treatment:

[1] No (skip to 5.4.2) [2] Not clear(skip to 5.4.2) [3] Yes

5.4.1.2.1 If[3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.4.2 Spinal cord compression syndrome

[1] Not appeared (skip to 5.4.3) [2] Not clear(skip to 5.4.3) [3] Appear

5.4.2.1 If [3], duration (month):

5.4.2.2 If [3], treatment:

[1] No (skip to 5.4.3) [2] Not clear(skip to 5.4.3) [3] Yes

5.4.2.2.1 If [3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.4.3 Brain metastases

[1] Not appeared (skip to 5.4.4) [2] Not clear(skip to 5.4.4) [3] Appear

5.4.3.1 If [3], duration (month):

5.4.3.2 If [3], treatment:

- 1
2
3 [1] No (skip to 5.4.4) [2] Not clear(skip to 5.4.4) [3] Yes
4 5.4.3.2.1 If [3], treatment effect:
5 [1] Improved [2] Progressed [3] Stable [4] Not clear
6
7 5.4.4 Meningeal metastases
8 [1] Not appeared (skip to 5.4.5) [2] Not clear(skip to 5.4.5) [3] Appear
9 5.4.4.1 If [3], duration (month):
10 5.4.4.2 If [3], treatment:
11 [1] No (skip to 5.4.5) [2] Not clear(skip to 5.4.5) [3] Yes
12 5.4.4.2.1 If [3], treatment effect:
13 [1] Improved [2] Progressed [3] Stable [4] Not clear
14
15 5.4.5 Pleural effusion
16 [1] Not appeared (skip to 5.4.6) [2] Not clear(skip to 5.4.6) [3] Appear
17 5.4.5.1 If [3], duration (month):
18 5.4.5.2 If [3], treatment:
19 [1] No (skip to 5.4.6) [2] Not clear(skip to 5.4.6) [3] Yes
20 5.4.5.2.1 If [3], treatment effect:
21 [1] Improved [2] Progressed [3] Stable [4] Not clear
22
23 5.4.6 Pyoperitoneum
24 [1] Not appeared (skip to 5.4.7) [2] Not clear(skip to 5.4.7) [3] Appear
25 5.4.6.1 If [3], duration (month):
26 5.4.6.2 If [3], treatment:
27 [1] No (skip to 5.4.7) [2] Not clear(skip to 5.4.7) [3] Yes
28 5.4.6.2.1 If [3], treatment effect:
29 [1] Improved [2] Progressed [3] Stable [4] Not clear
30
31 5.4.7 Pericardial effusion
32 [1] Not appeared(skip to 5.4.8) [2] Not clear(skip to 5.4.8) [3] Appear
33 5.4.7.1 If [3], duration (month):
34 5.4.7.2 If [3], treatment:
35 [1] No (skip to 5.4.8) [2] Not clear(skip to 5.4.8) [3] Yes
36 5.4.7.2.1 If [3], treatment effect:
37 [1] Improved [2] Progressed [3] Stable [4] Not clear
38
39 5.4.8 Intestinal obstruction
40 [1] Not appeared(skip to 5.4.9) [2] Not clear(skip to 5.4.9) [3] Appear
41 5.4.8.1 If [3], duration (month):
42 5.4.8.2 If [3], treatment:
43 [1] No (skip to 5.4.9) [2] Not clear(skip to 5.4.9) [3] Yes
44 5.4.8.2.1 If [3], treatment effect:
45 [1] Improved [2] Progressed [3] Stable [4] Not clear
46
47 5.4.9 Pain
48 [1] Not appeared (skip to 5.4.10) [2] Not clear(skip to 5.4.10) [3] Appear
49 5.4.9.1 If [3], duration (month):
50 5.4.9.2 If [3], treatment:
51 [1] No (skip to 5.4.10) [2] Not clear(skip to 5.4.10) [3] Yes
52 5.4.9.2.1 If [3], treatment effect (site and score):
53
54
55
56
57
58
59
60

5.4.10 Cerebral thrombosis/ hemorrhage

[1] Not appeared (skip to 5.4.11) [2] Not clear(skip to 5.4.11) [3] Appear

5.4.10.1 If [3], duration (month):

5.4.10.2 If [3], treatment:

[1] No (skip to 5.4.11) [2] Not clear(skip to 5.4.11) [3] Yes

5.4.10.2.1 If [3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.4.11 Interstitial pneumonia

[1] Not appeared(skip to 5.4.12) [2] Not clear(skip to 5.4.12) [3] Appear

5.4.11.1 If [3], duration (month):

5.4.11.2 If [3], treatment:

[1] No (skip to 5.4.12) [2] Not clear(skip to 5.4.12) [3] Yes

5.4.11.2.1 If [3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.4.12 Pulmonary embolism

[1] Not appeared(skip to 5.4.13) [2] Not clear(skip to 5.4.13) [3] Appear

5.4.12.1 If [3], duration (month):

5.4.12.2 If [3], treatment:

[1] No (skip to 5.4.13) [2] Not clear(skip to 5.4.13) [3] Yes

5.4.12.2.1 If [3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.4.13 Cardiac insufficiency

[1] Not appeared(skip to 5.4.14) [2] Not clear(skip to 5.4.14) [3] Appear

5.4.13.1 If [3], duration (month):

5.4.13.2 If [3], treatment:

[1] No (skip to 5.4.14) [2] Not clear(skip to 5.4.14) [3] Yes

5.4.13.2.1 If [3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.4.14 Arrhythmia

[1] Not appeared(skip to 5.4.15) [2] Not clear(skip to 5.4.15) [3] Appear

5.4.14.1 If [3], duration (month):

5.4.14.2 If [3], treatment:

[1] No (skip to 5.4.15) [2] Not clear(skip to 5.4.15) [3] Yes

5.4.14.2.1 If [3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.4.15 Hypercoagulable state

[1] Not appeared (skip to 5.5) [2] Not clear(skip to 5.5) [3] Appear

5.4.15.1 If [3], duration (month):

5.4.15.2 If [3], treatment:

[1] No (skip to 5.5) [2] Not clear(skip to 5.5) [3] Yes

5.4.15.2.1 If [3], treatment effect:

[1] Improved [2] Progressed [3] Stable [4] Not clear

5.5 Other procedures

5.5.1 Interdisciplinary consultation

- [1] No (skip to 5.5.2) [2] Not clear(skip to 5.5.2) [3] Yes
- 5.5.1.1 Disciplines involved
- [1] Neurology [2] Infectious diseases [3] Nephrology
- [4] Endocrinology [5] Cardiovascular diseases
- [6] Others (specify)

5.5.1.2 Total times of consultation:

5.5.2 Psychological/behavioral intervention

- [1] No (skip to 5.5.3) [2] Not clear(skip to 5.5.3) [3] Yes

5.5.2.1 Type of interventions performed

- [1] Neurology [2] Infectious diseases [3] Nephrology
- [4] Endocrinology [5] Cardiovascular diseases
- [6] Others (specify)

5.5.2.2 Total sessions of intervention performed:

5.5.3 Traditional Chinese medicine used

- [1] No (skip to 10.1) [2] Not clear(skip to 10.1) [3] Yes

5.5.2.1 Regimen of TCM used (specify):

5.5.2.2 Duration of TCM use (days):

Part F: Charges on the inpatient care

6.1 Total inpatient care fee:

6.2 Registration fee

6.3 Bed fee

6.4 Examination fee

6.5 Treatment fee

6.6 Operation fee

6.7 Laboratory fee

6.8 Nursing fee

6.9 Medicines fee

6.10 Other fee

Name of data extractor:

Date of data extraction(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

Part B: Patient's diagnostic and treatment procedures

2.1: When were you (or was he/she) first diagnosed with lung cancer?

Date of diagnosis (dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|

2.2: Have you (or Has he/she) been hospitalized due to the lung cancer?

[1] Yes [2] No (skip to 3) [3] Not clear (skip to 3)

2.3: If yes, please tell me, one-by-one, where and when were (or was) you (or he/she) hospitalized due to the lung cancer and how much it costed respectively.

No.	Name of hospital	Admission Date (mm-yyyy)	Total expenditure(RMB)
[1]			
[2]			
[3]			
[4]			
[5]			
[6]			
[7]			
[8]			
[9]			

(Please add more lines as necessary)

2.4: Have you (or Has he/she) sought outpatient treatment for the lung cancer?

[1] Yes [2] No (skip to 3) [3] Not clear (skip to 3)

2.5: If yes, please tell me, one-by-one, where and when had (or was) you (or he/she) received outpatient treatment; what type of treat and how much it costed respectively.

No.	Name of hospital	Date (mm-yyyy)	Type of treatment	Total expenditure(RMB)
[1]				
[2]				
[3]				
[4]				
[5]				
[6]				
[7]				
[8]				
[9]				

(Please add more lines as necessary)

2.6: Have you (or Has he/she) sought medical checkups for monitoring development of the lung cancer?

[1] Yes [2] No (skip to 4) [3] Not clear (skip to 4)

2.7: If yes, please tell me, one-by-one, where and when did the checkup happen and what were the findings respectively

No.	Name of hospital	Date of checkup (mm-yyyy)	Reoccurrence	Metastasis
[1]				
[2]				
[3]				

1
2
3 [4]

4 [5]

5 [6]

6 [7]

7 [8]

8 [9]

9 (Please add more lines as necessary)

10
11
12
13
14 2.8: How are you (is he/she) now?

15 [1] Alive

[2] Deceased

16 2.6.1: If [2], when did it happen (dd-mm-yyyy) ? |_|_|-|_|_|-|_|_|_|_|

17
18 2.9: In addition to the inpatient care and medical checkups mentioned above, have you (or has he/she)
19 tried other measures to cure the lung cancer?

20 [1] Yes

[2] No (skip to ending)

[3] Not clear (skip to ending)

21
22 3.0: If yes, please tell me, one-by-one, what is it and how often it has/had been?

No.	Name of practice	Description of practice	Frequency	Length (months)
23	[1]			
24	[2]			
25	[3]			
26	[4]			
27	[5]			
28	[6]			
29	[7]			
30	[8]			
31	[9]			

23 [1]

24 [2]

25 [3]

26 [4]

27 [5]

28 [6]

29 [7]

30 [8]

31 [9]

32 (Please add more lines as necessary)

33
34
35
36
37
38 Name of data extractor:

39 Date of data extraction(dd-mm-yyyy): |_|_|-|_|_|-|_|_|_|_|:

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Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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ABSTRACT

Introduction: Routine inpatient care (RIC) for cancer patients forms various pathways of clinical procedures. Although most of the individual procedures comprising the pathways have been tested via clinical trials, little is known about the collective cost and effectiveness of the pathways as a whole. This study aims at examining RIC pathways for lung cancer patients from rural Anhui, China and their determinants and economic impacts.

Methods and analysis: The study adopts a retrospective cohort study design and proceeds in 5 steps. Step 1 defines 4 main categories of study variables including clinical procedures, direct cost and effectiveness of procedures, and factors affecting use of these procedures and their cost and effectiveness. Step 2 selects a cohort of 5000 lung cancer patients diagnosed between July 1, 2014 and June 30, 2015 from rural Anhui by clustered-random sampling. Step 3 retrieves the records of all the inpatient care episodes due to the lung cancer and extracts data about RIC procedures, proximate variables (e.g., Karnofsky performance status, lung function score) of patient outcomes and related factors (e.g., stage of cancer, age, gender) by 2 independent clinician researchers using a web-based form. Step 4 estimates the direct cost of each of the RIC procedures using micro-costing and collects data about ultimate patient outcomes (survival and progression-free survival) through a follow up survey of patients and/or their close relatives. Step 5 analyzes data collected and explores pathways of RIC procedures and their relations with patient outcomes, costs, cost-effect ratios and a whole range of clinical and socio-demographic factors using multivariate regression and path models.

Ethics and dissemination: The study protocol has been approved by authorized ethics committee of Anhui Medical University (reference number: 20170312). Findings from the study will be disseminated through conventional academic routes such as peer-reviewed publications and presentations at regional, national and international conferences.

Trial registry

ISRCTN25595562

Key words: cost effectiveness, lung cancer, inpatient care, retrospective study, China

Strengths and limitations of this study

- The study adopts a retrospective cohort study design involving a large representative sample of community patients;
- It provides data for determining the cost-effectiveness of different treatment approaches as a whole rather than individual procedures;
- It examines pathways of routine inpatient care for a huge but understudied Chinese rural population;
- It extracts data from routine records kept at different hospitals and thus suffers from discrepancies in performances and data qualities.

Introduction

Lung cancer has been the most common cancer in the world for several decades.¹ Estimated new cases of the disease was 1.8 million in 2012 (12.9% of the total), 58% of which occurred in less developed regions. It was also the most common cause of death from cancer worldwide, being responsible for nearly one in five (1.59 million in absolute number) of the total.² In China, lung cancer incidence showed a slight decreasing trend in the past few years, particularly for males. However, it is still the top first cancer for males and second for females, accounting for 25.2% of all new cancer cases and 29.5% of all cancer deaths in 2012.³

Routine inpatient care (RIC) for lung cancer consists of a combination of procedures. Patients with possible lung cancer need a detailed history and physical examination first. Then they should undergo posterior-anterior and lateral chest radiographs as well as CT scans of the chest and abdomen. In order to further confirm and determine stage and histology of the lesion, other diagnostic methods needed include whole-body fluoro-deoxy-glucose positron emission tomography, endoscopic ultrasound, sputum cytology, fine-needle aspiration, bronchoscopy etc. Following diagnosis of lung cancer, the patients proceed with combined-modality therapies depending on stage of the disease and co-morbidities and complications. Historically, surgery provides the best chance for cure for patients whose lung cancers are limited to the hemithorax and can be totally encompassed by excision.^{4 5} Surgery has been generally used in combination with external-beam radiotherapy for control of the primary tumor and regional lymphatics.⁶ In addition, chemotherapy has also been advocated as an integral part of combined modality approaches to earlier stages of disease.^{7 8} For unselected advanced none-small cell lung cancer, platinum-based combinations have become the standard of care; while cisplatin- or carboplatin-based doublets are standard for patients with stage IV disease.^{9 10} More recently, EGFR tyrosine kinase inhibitors have been introduced in second- and third-line treatment of advanced disease and in first-line treatment for selected patients.¹¹

Given the complex procedures, ensuring quality RIC for lung cancer patients has been most challenging and guidelines are widely used in addressing this challenge. Numerous

1
2
3 studies have documented positive relations between compliance with guidelines and
4 patient outcomes.^{12 13} However, researchers have also raised concerns about guidelines.
5 One of such concerns refers to lack of adequate consideration of costs. Most clinical
6 procedures not only affect disease outcomes but also incur considerable costs.^{14 15} Yet
7 guidelines are based on trials focused primarily on effectiveness (e.g., survival) with little
8 attention being paid to economic consequences.¹⁶ Another concern relates to
9 incompatible population between clinical trials and RIC. Clinical trials on which
10 guidelines are based use highly selected populations; while RIC serves a general lung
11 cancer population with different age, performance status and comorbidities.^{17 18} A third
12 concern revolves uncertain interactions between procedures. Although most individual
13 guideline recommended procedures (GRPs) have established evidences, they are not used
14 in isolation but in conjunction with others forming various clinical combinations. Efforts
15 systematically assessing and comparing these combinations are scarce.¹⁹⁻²² A fourth
16 concern originates from varied compliance with guidelines since RIC often deviates
17 substantially from guidelines.^{23 24} The cost-effectiveness of these “substandard” or mixed
18 combinations of procedures (partly from guidelines, partly from experiences of
19 individual clinicians) falls far from well-understood.²⁵ These all point to a clear need for
20 evaluating RIC even though guidelines are widely available.
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27 All the above concerns are most pertinent to China. First, China has a unique “dual”
28 medical care system in which patients often receive western medicine and traditional
29 Chinese medicine simultaneously or in turn.²⁶ Second, China lacks coordinated referral
30 and follow up mechanisms and cancer patients often moves freely from one hospital to
31 another for different rounds of inpatient cancer care.²⁷ This makes it hard for clinicians in
32 leveraging different inpatient care episodes at different time points and hospitals into
33 continuous and synergetic service. Third, China has strong socio-cultural norms and
34 financial incentives that hinder cost control and guideline compliance.²⁸
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39 **Study aims**

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42 This study aims at identifying main pathways of RIC procedures for lung cancer patients
43 from rural Anhui, China and examining determinants of the pathways and economic
44 impacts. Specific questions to be addressed include: a) what combinations of diagnosis
45 and treatment procedures (or pathways for short) an individual patient may experience
46 during all his/her hospitalization episodes due to lung cancer-related problems; b) which
47 are the most and least frequent pathways; c) what determines the flow among these
48 pathways; d) which are the most and least cost-effective pathways in relation to the other
49 pathways; and e) what factors are associated with the relative cost-effectiveness.
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51
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53 The above “pathways” of inpatient care means combinations of diagnosis and treatment
54 procedures an individual patient may experience during all his/her hospitalization
55 episodes due to lung cancer-related problems. Suppose a lung cancer patient experienced
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6 times/rounds of hospitalized care and during each of these hospitalization episodes, the patient underwent several diagnosis and treatment procedures, all these procedures form the “pathway” of this particular patient.

Methodology

Identification of procedures

The study uses a self-designed and web-based data extraction form in identifying major clinical procedures described in any RIC record under concern. The form lists all major RIC procedures under two main domains, i.e., diagnostic procedures (e.g., chest X-ray, chest CT, neck ultrasonography) and treatment procedures (e.g., surgical therapy, chemotherapy, psycho-behavioral intervention).

Estimation of costs

The study estimates overall and categorical costs (direct costs only) for each of the RIC procedures (e.g., lung function examination, computed tomography, white blood cell count) identified above using micro-costing techniques.^{29 30} Taking the example of lung function examination, categorical costs include costs on personnel, equipment, materials, reagents and others needed in completing the examination; while overall cost of the procedure equals the sum of all these categorical costs. In addition, the study also calculates overall cost on individual inpatient by adding up the overall costs on all the clinical procedures he/she has received.

Measurement of effectiveness

The study uses both proximal variables of outcomes (PV) and ultimate outcome (UO) measures of effectiveness of RIC procedures. The UO indicators derive from a follow up survey about 2 years and half after the first hospitalization and include overall survival (OS), progression-free survival (PFS), quality of life (QoL), and quality adjusted life years (QALYs). Here, QoL is assessed using the widely recognized EQ-5D-5L instrument.³¹

The PV measures come from RIC records and include Eastern Cooperative Oncology Group (ECOG), Karnofsky performance status (KPS) and compiled scores of: a) symptoms (e.g., chronic cough, chest pain, wasting syndrome); b) lung functions (e.g., forced vital capacity, forced one second expiratory volume), c) image findings (e.g., number of nodules identified in the lung, size of the largest nodules, presence of pleura or pericardial effusion). Each of these domain specific PV scores equals weighted sum of all sub-indicators within the domain. For example, the compiled score of “lung functions” equals the sum of weighted values of forced vital capacity, forced one second expiratory volume etc. Here the weights come from the coefficients of multivariate regression modeling using an UO indicator (e.g., OS) as the dependent variable; while forced vital

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3 capacity, forced one second expiratory volume etc. as the independent variables; and
4 stage of disease, age, gender and others as the confounding variables.
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6 **Calculation of cost-effectiveness**

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8 The study adopts relative cost-effectiveness ratios (RCERs) and incremental cost-
9 effectiveness ratios (ICERs) as the main indicators for measuring cost-effectiveness.
10 Here ICER is defined by the difference in cost between two selected sets of RIC
11 procedures, divided by the difference in their effect. More specifically, $ICER = (C_{r+x} -$
12 $C_r)/(E_{r+x} - E_r)$, where C_r and E_r is the cost and effect in the reference group and
13 C_{r+x} and E_{r+x} , the cost and effect in the group who have underwent all the procedures in
14 the reference group plus x, a specific procedure under concern.³² Suppose, x represents a
15 commonly used traditional Chinese medicine (TCM) which incurs 100 dollars; while r, a
16 typical combination of diagnosis and treatment procedures without the TCM. The
17 combination without the TCM costs 1000 dollars and the survival time of patients who
18 have adopted this combination is 1.5 years on average; while the same figure for patients
19 who have used the combination plus the TCM is 1.51. Then the $C_{r+x} = 1000 + 100 =$
20 1100 dollars and the $ICER$ of the TCM = $(1100-100)/(1.51-1.5)=10000$ dollars per life
21 year saved. Similarly, $RCER = (C_{r+x}/E_{r+x})/(C_r/E_r) = (1100/1.51)/ (1000/1.50) =$
22 1.09 .
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28 **Identification of influencing factors**

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30 The study also extracts, from RIC records, data about patient factors commonly believed
31 to be linked with disease progression, treatment response and outcomes and utilization of
32 RIC procedures. These include: a) socio-demographics (e.g., age, gender, body height
33 and weight, education, employment, marital status, medical insurance); b) risk behaviors
34 and histories (e.g., smoking, alcohol drinking, history of cancer among family members);
35 c) historical and biological test findings (e.g., value of ALK, KRAS, EGFR, PDL1, CEA,
36 CA125, proGRP); d) comorbidities and complications (e.g., presence of superior vena
37 cava syndrome, brain metastases) and stage of disease. Here, disease staging uses TNM
38 system and this staging will be treated as the most important factor throughout the data
39 analysis especially in its effects on the flow of different pathways and their RCER/ICER.
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44 **Selection of participants**

45
46 The study is implemented in Anhui, an inland province located in middle and east China.
47 It has a population of 61.4 million and its per capita GDP and income rank in the middle
48 (the 14th) among all provinces in the nation.^{33 34} Its social, cultural and economic
49 background is representative of over 80% of the whole population in China.^{33 34} The
50 province has 68 rural counties and each of them divides into 10 to 20 townships.
51 Selection of participating counties, townships, patients and RIC case records uses a
52 clustered random sampling which proceeds in 5 steps. Step 1 classifies all the counties in
53 Anhui into southern, northern and middle areas. Step 2 randomly selects 3 counties from
54 each of these areas (12 counties in total). Step 3 randomly draws 4 townships from each
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3 of the counties selected (48 townships in total). Step 4 searches the provincial
4 reimbursement database of the New Rural Cooperative Medical System (NRCMS) and
5 identifies all the patients within the selected townships who had been first diagnosed with
6 primary lung cancer during July 1, 2014 and June 30, 2015. Step 5 searches the database
7 again for all episodes of hospitalization due to the lung cancer for the patients identified
8 in step 4. NRCMS covers 98% of the rural residents and the estimated number of patients
9 and admission episodes is about 5,000 and 25,000 respectively.
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13 The above sample size was determined by our study purpose of building multivariate
14 models of factors affecting the flow among and RCER/ICER of specific RIC pathways.
15 Lung cancer patients generally receive 4 to 6 rounds of inpatient care. Given the various
16 diagnostic and treatment procedures available, there are hundreds of potential RIC
17 pathways (combinations of diagnosis and treatment procedures from the first to the last
18 round of RIC). We plan to group these pathways into manageable (around 20) categories
19 depending on the resultant distribution of the actual pathways and we aim to enter 20-30
20 factors into the multivariate models for each of these categorical pathways. Based on
21 these pre-conditions and that the sample size of a multi-variable model should generally
22 be 10 times the number of independent variables, we need 250 patients for each pathway.
23 This translates into 5000 patients in total.
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28 **Data collection**

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30 The study obtains data through follow-up survey and data extraction. The follow-up
31 survey applies to all the lung cancer patients identified above. It solicits information
32 about the patient's: a) disease progression (i.e., died, alive with or without progression);
33 b) if died, date of death; c) additional admissions due to the lung cancer not included in
34 the above mentioned NRCMS database. The survey uses a short structured questionnaire.
35 Administration of the questionnaire starts with a telephone interview (of the patient under
36 concern or his/her close relatives for up to 5 time attempts) followed by a face-to-face
37 interview (of the same respondents for up to 2 attempts) if the telephone contacts have
38 failed. The recruitment strives to reach over 85% rate of participation. And the
39 researchers are trained to record reasons of attrition for each of the patients they have lost
40 so as to allow for assessing potential biases. The data extraction applies to records of all
41 the hospital admission episodes identified via the NRCMS database and the follow up
42 survey. It uses a structured web-based form and extracts data about the clinical
43 procedures, costs, effectiveness and influencing factors described above. Two
44 experienced clinicians on care of lung cancer perform the data extraction. They visit (on
45 one-by-one base) all the relevant hospitals, ask for permission to examine the full records
46 and fill the worksheet independently first followed by discussions, if applicable, to solve
47 discrepancies.
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Data analysis

The data collected above allow a variety of descriptive and multivariate analysis concerning the costs and effectiveness of RIC. The effectiveness analysis comprises all the UO indicators mentioned above including progression free survival, overall survival, quality of life and DALYs. For each of these UO indicators, the analysis will produce: a) estimation of average rates or values with 95% confidence intervals at different time points after first diagnosis by disease stage, PV indicators, RIC pathways, non-hospital care categories, age range etc.; b) multivariate regression models using similar variables as independent variables; and c) path models using disease stage, RIC pathways, non-hospital care categories, age range etc. as exogenous, complied PV indices as direct endogenous, and individual PV indicators as indirect endogenous variables (Figure 1a). Area under ROC (receiver operating characteristic) curve will be calculated for assessing the predictability of models using binary classifier as the dependent variable (e.g., models of progression free survival, overall survival).

The cost analysis explores mainly: a) overall and categorical costs on different rounds of hospitalization by socio-demographic and selected clinical conditions (Figure 2); b) scatter plot of RIC procedures using the occurrence rate and unit cost of individual procedures as the coordinates; c) multivariate regression models of overall and selected categorical costs using disease stage, PV indicators, RIC pathways, non-hospital care categories, age range etc. as independent variables; and d) Markov models of mean cost for managing lung cancer patients (Figure 1b).

The cost-effectiveness analysis focuses primarily on constructing a pathway tree to help estimate expected overall and pathway specific cost, effectiveness and identify pathways with the highest or lowest RCER/ICER. The tree consists of different branches of combinations of RIC procedures starting from the first to the last episode of inpatient care labeled with estimated costs and possibilities along the pathways and outcomes at the end of the pathways (Figure 3). Relevance of the pathway tree is tested by means of, for instance, varying the percentage of patient flowing among the different pathways or the costs of major diagnostic and treatment procedures consisting the braches and then examining changes in the ranking of the pathways in terms of relative cost-effectiveness. The analysis also pays particular attention to identifying as many as comparable pairs of RIC pathways as possible and calculating RCERs/ICERs accordingly in a hope to uncover potential pathways with practice, policy and research implications.

The pathway tree construction will use TreeAge³⁵; while the descriptive and multivariate model analysis, SPSS 16. Cases with missing data about a specific item will be excluded from the analysis involving the item and where applicable, the statistical null hypothesis is be rejected at the significance level of $\alpha = 0.05$.

Ethics and dissemination

The study protocol had been reviewed and approved by the Biomedical Ethics Committee of Anhui Medical University (reference number: 20170312). Participation of hospitals, patients and their relatives are voluntary and written informed consent is required for all participants. Findings from the study will be disseminated through conventional academic routes such as peer-reviewed publications and presentations and regional, national and international conferences.

Discussion

The study would share the experience of lung cancer care from the rural Chinese perspective. It is an important sharing of knowledge on population-based lung cancer care, since most economic evidence comes from Europe and North America. In China, traditional Chinese medicine is used to complement or replace western medicine. This results in quite different pathways of lung cancer care that have seldom been well explored in published literatures. China has a long history of almost no charges being made for clinical consultations and most patients are used to paying only for medicines, laboratory tests and equipment-based examinations. This forms a perverse financial incentive for clinicians for ordering more sophisticated examinations and tests and for over prescribing. China's lack of referral and follow up mechanisms also merits particular attention. As an individual patient changes from one hospital (say for the first round of treatment) to another (for the second round treatment), he/she may receive different treatment regimens. Discontinued treatment and follow up may make it hard for clinicians to base their treatment decisions on observed effects.

Perhaps the most noteworthy findings of the current study may be the description of the pathways of RIC procedures and their economic impacts (Figure 2). These pathways will provide easily understandable means for estimating and identifying, among others, the following: a) which pathways or combinations of procedures happen most or least in routine practice during different rounds of hospitalization for inpatients suffering from lung cancer in rural China; b) which pathways (from the first to last round of hospitalization) incur the highest or lowest direct costs; and c) which pathways result in the best or worst patient outcome in terms of different UO measures. These have important implications for clinical decision-making as well as policy-making.

Another point worth mentioning in particular refers to the links between the domain specific proximate (PV) indices to key ultimate outcome (UO) indicators (e.g., OS, PFS, QALYs) generated via a large scale (involving 5000 lung cancer patients) retrospective cohort study. They provide useful references for clinicians on care of lung cancer patients in selecting appropriate procedures to achieve optimal collective contributions to UO.³⁶ At present, although PV indicators are observed routinely, they are presented to clinicians as individual indicators rather than compiled indices. And given the large

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3 number of PV indicators involved and the complex relations between RIC procedures
4 and PV indicators and then UO indicators, it is difficult for practicing clinicians to make
5 balanced decisions upon their personal experiences.³⁷
6

7
8 In addition, this study addresses RIC for lung cancer at hospitals in China from a range
9 of meaningful perspectives. The study reinforces the concepts introduced in the landmark
10 studies of Fisher et al and Wennberg et al, which convincingly demonstrated that high
11 quality was not necessarily associated with high cost.³⁸ Describing inpatient lung cancer
12 care in a view that its value is directly proportional to outcomes and inversely
13 proportional to costs helps in guiding quality improvement by either better outcomes
14 and/or lower costs.³⁹ The study calculates and compares the collective costs and
15 effectiveness of different RIC pathways as a whole and thus informs coordinated
16 inpatient care episodes and procedures at different time points and hospitals. The study
17 enables RCER/ICER estimation for specific guideline recommended procedures (GRPs)
18 using various combinations of real and uncontrollable RIC procedures as the reference
19 and thus enhances understanding and application of GRPs established through well-
20 controlled studies in routine practice contexts.
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26 The study also has limitations. The first limit concerns data reliability. Although the
27 majority of data are extracted from RIC records kept at hospitals, the study uses self-
28 reported data about quality of life and inpatient, outpatient and home care. Self-reports
29 are prone to various biases including recall problems particularly among the elderly, over
30 or under reporting by the respondents for reasons like perceived expectations from the
31 researchers or for fearing of potential worries or distress. These biases may be reduced to
32 a minimum in our study by means of interviewer training, use of chorological recall and
33 probing techniques, and cross-checks of findings from patient interviews, health
34 insurance database and hospital records. More importantly, the study uses EQ-5D-5L in
35 assessing quality of life. It has already been tested with adequate reliability both
36 internationally and in China. Regarding non-hospitalized care, the study asks only simple
37 questions about what kind of care the patients have experienced and when and for how
38 long. These questions are relatively memorable and easy to answer. The second limit
39 relates to selective study content. The study considers only inpatient care; while patients
40 may use various self-treatment and outpatient treatment in addition to inpatient care.^{40 41}
41 Inpatient and non-inpatient treatment may substitute each other to some extent. These
42 may result in under-estimation of the effectiveness of RIC procedures. Fortunately, this
43 under-estimation may be offset to a large extent by treating non-hospital care as
44 confounders and the study data to be collected allow this exercise. Third, the study
45 considers only direct costs rather than full costs taking both direct and indirect costs into
46 consideration. In addition, different hospitals use different equipment, reagents and
47 medicines. Their quality of case records may also vary substantially. These raise
48 compatibility concerns in pooling data from different hospitals together and performing
49 aggregate analysis. Finally, readers may raise concerns about representativeness of
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3 inpatients to the larger cancer patients. Hospitalization rates documented from other
4 countries vary greatly;⁴² while similar data from China are scarce. Our estimation, using
5 the dataset of the last province-wide Household Health Survey of Anhui, of the
6 proportion of lung cancer patients who had been admitted to hospitals at least once was
7 as high as 89%.⁴³
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10 **Competing interests**

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13 The authors declare no competing interests.
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16 **Authors' contributions**

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18 XS and MD contributed equally in conceiving this project, facilitating protocol and
19 instrument development, and drafting this manuscript. RF, ML, PZ and TJ are core
20 researchers for cost estimation, record extraction, follow up survey and data analysis
21 respectively. DW provided expertise for overall design of the study, and revised and
22 finalized the manuscript. All authors have read and approved the final submission.
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3 Figure 1 Schematic structure of sample multivariate models to be built
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5 Figure 2 Simulated cost by selected socio-demographics and clinical characteristics
6 (TC=total cost; KRMB=1000 Chinese yuan)
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8 Figure 3 Anticipated “procedure-outcome” tree of inpatient lung cancer care (Tx = the xth
9 round of hospitalization; Cx = the xth combination of clinical procedures; Px = possibility
10 of using the xth combinations of clinical procedures; Ox = the xth patient outcome
11 index/indicator)
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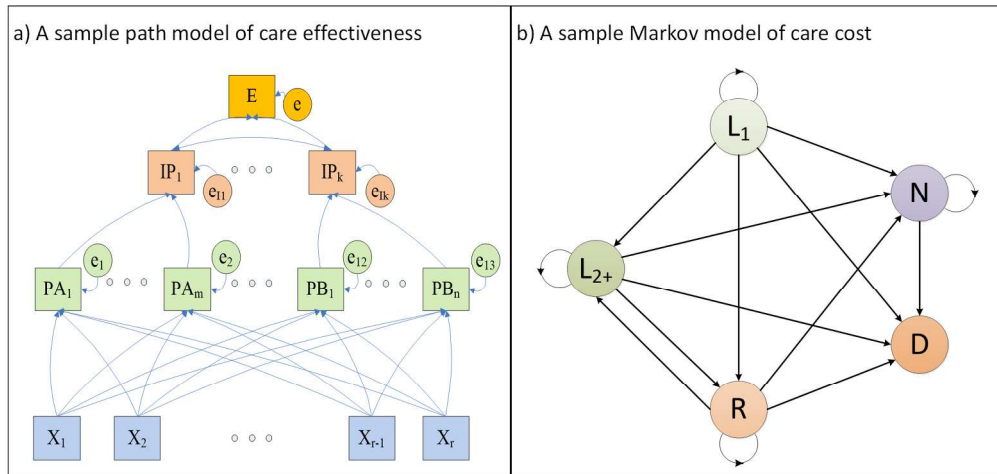


Figure 1 Schematic structure of sample multivariate models to be built/ X=independent variables; PA or PB=domain A or proximate indicators of effectiveness; IP=index of proximate variables; e=systematic error; and E= effectiveness, e.g., overall survival, QALYs; L₁=first line treatment; L₂₊=second or third line treatment; R=remission; N=no active treatment; D=death.

188x88mm (300 x 300 DPI)

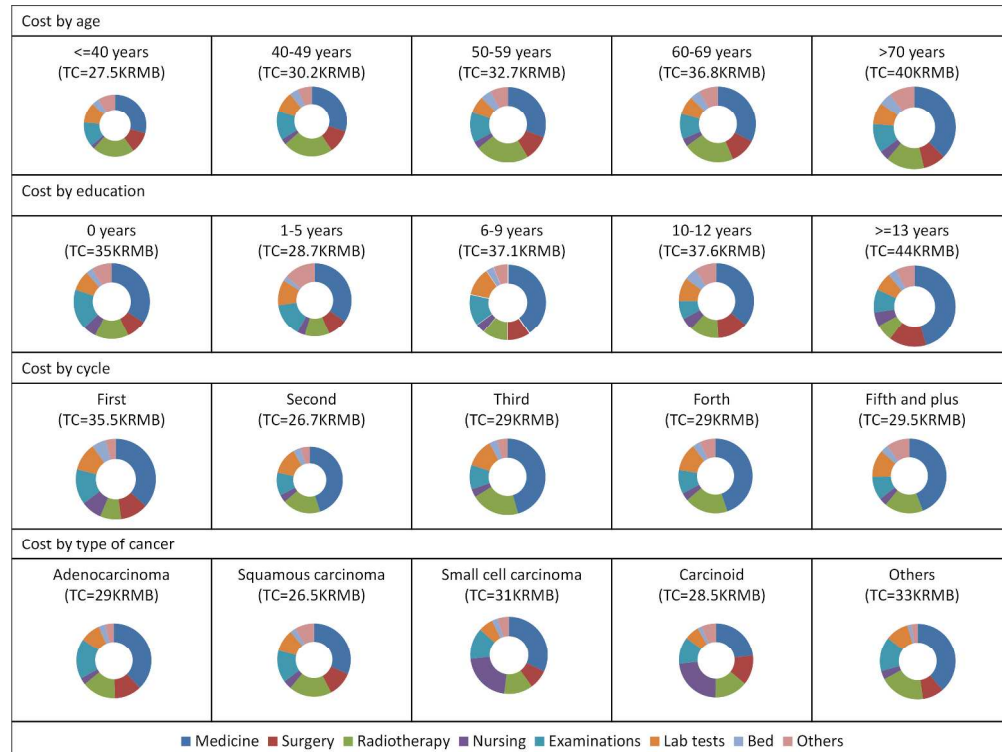


Figure 2 Simulated cost by selected socio-demographics and clinical characteristics (TC=total cost; KRMB=1000 Chinese yuan)

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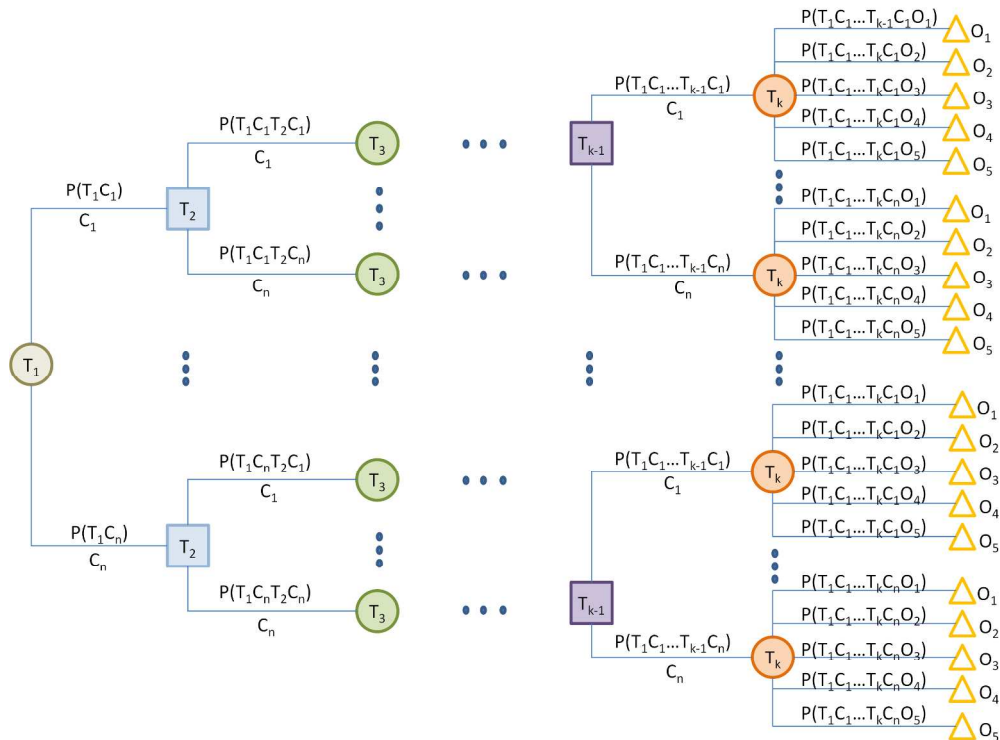


Figure 3 Anticipated "procedure-outcome" tree of inpatient lung cancer care (T_x = the x^{th} round of hospitalization; C_x = the x^{th} combination of clinical procedures; P_x = possibility of using the x^{th} combinations of clinical procedures; O_x = the x^{th} patient outcome index/indicator)

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Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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ABSTRACT

Introduction: Routine inpatient care (RIC) for cancer patients forms various pathways of clinical procedures. Although most of the individual procedures comprising the pathways have been tested via clinical trials, little is known about the collective cost and effectiveness of the pathways as a whole. This study aims at examining RIC pathways for lung cancer patients from rural Anhui, China and their determinants and economic impacts.

Methods and analysis: The study adopts a retrospective cohort study design and proceeds in 5 steps. Step 1 defines 4 main categories of study variables including clinical procedures, direct cost and effectiveness of procedures, and factors affecting use of these procedures and their cost and effectiveness. Step 2 selects a cohort of 5000 lung cancer patients diagnosed between July 1, 2014 and June 30, 2015 from rural Anhui by clustered-random sampling. Step 3 retrieves the records of all the inpatient care episodes due to the lung cancer and extracts data about RIC procedures, proximate variables (e.g., Karnofsky performance status, lung function score) of patient outcomes and related factors (e.g., stage of cancer, age, gender) by 2 independent clinician researchers using a web-based form. Step 4 estimates the direct cost of each of the RIC procedures using micro-costing and collects data about ultimate patient outcomes (survival and progression-free survival) through a follow up survey of patients and/or their close relatives. Step 5 analyzes data collected and explores pathways of RIC procedures and their relations with patient outcomes, costs, cost-effect ratios and a whole range of clinical and socio-demographic factors using multivariate regression and path models.

Ethics and dissemination: The study protocol has been approved by authorized ethics committee of Anhui Medical University (reference number: 20170312). Findings from the study will be disseminated through conventional academic routes such as peer-reviewed publications and presentations at regional, national and international conferences.

Trial registry

ISRCTN25595562

Key words: cost effectiveness, lung cancer, inpatient care, retrospective study, China

Strengths and limitations of this study

- The study adopts a retrospective cohort study design involving a large representative sample of community patients;
- It provides data for determining the cost-effectiveness of different treatment approaches as a whole rather than individual procedures;
- It examines pathways of routine inpatient care for a huge but understudied Chinese rural population;
- It extracts data from routine records kept at different hospitals and thus suffers from discrepancies in performances and data qualities.

Introduction

Lung cancer has been the most common cancer in the world for several decades.¹ Estimated new cases of the disease was 1.8 million in 2012 (12.9% of the total), 58% of which occurred in less developed regions. It was also the most common cause of death from cancer worldwide, being responsible for nearly one in five (1.59 million in absolute number) of the total.² In China, lung cancer incidence showed a slight decreasing trend in the past few years, particularly for males. However, it is still the top first cancer for males and second for females, accounting for 25.2% of all new cancer cases and 29.5% of all cancer deaths in 2012.³

Routine inpatient care (RIC) for lung cancer consists of a combination of procedures. Patients with possible lung cancer need a detailed history and physical examination first. Then they should undergo posterior-anterior and lateral chest radiographs as well as CT scans of the chest and abdomen. In order to further confirm and determine stage and histology of the lesion, other diagnostic methods needed include whole-body fluoro-deoxy-glucose positron emission tomography, endoscopic ultrasound, sputum cytology, fine-needle aspiration, bronchoscopy etc. Following diagnosis of lung cancer, the patients proceed with combined-modality therapies depending on stage of the disease and co-morbidities and complications. Historically, surgery provides the best chance for cure for patients whose lung cancers are limited to the hemithorax and can be totally encompassed by excision.^{4 5} Surgery has been generally used in combination with external-beam radiotherapy for control of the primary tumor and regional lymphatics.⁶ In addition, chemotherapy has also been advocated as an integral part of combined modality approaches to earlier stages of disease.^{7 8} For unselected advanced none-small cell lung cancer, platinum-based combinations have become the standard of care; while cisplatin- or carboplatin-based doublets are standard for patients with stage IV disease.^{9 10} More recently, EGFR tyrosine kinase inhibitors have been introduced in second- and third-line treatment of advanced disease and in first-line treatment for selected patients.¹¹

Given the complex procedures, ensuring quality RIC for lung cancer patients has been most challenging and guidelines are widely used in addressing this challenge. Numerous

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3 studies have documented positive relations between compliance with guidelines and
4 patient outcomes.^{12 13} However, researchers have also raised concerns about guidelines.
5 One of such concerns refers to lack of adequate consideration of costs. Most clinical
6 procedures not only affect disease outcomes but also incur considerable costs.^{14 15} Yet
7 guidelines are based on trials focused primarily on effectiveness (e.g., survival) with little
8 attention being paid to economic consequences.¹⁶ Another concern relates to
9 incompatible population between clinical trials and RIC. Clinical trials on which
10 guidelines are based use highly selected populations; while RIC serves a general lung
11 cancer population with different age, performance status and comorbidities.^{17 18} A third
12 concern revolves uncertain interactions between procedures. Although most individual
13 guideline recommended procedures (GRPs) have established evidences, they are not used
14 in isolation but in conjunction with others forming various clinical combinations. Efforts
15 systematically assessing and comparing these combinations are scarce.¹⁹⁻²² A fourth
16 concern originates from varied compliance with guidelines since RIC often deviates
17 substantially from guidelines.^{23 24} The cost-effectiveness of these “substandard” or mixed
18 combinations of procedures (partly from guidelines, partly from experiences of
19 individual clinicians) falls far from well-understood.²⁵ These all point to a clear need for
20 evaluating RIC even though guidelines are widely available.
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27 All the above concerns are most pertinent to China. First, China has a unique “dual”
28 medical care system in which patients often receive western medicine and traditional
29 Chinese medicine simultaneously or in turn.²⁶ Second, China lacks coordinated referral
30 and follow up mechanisms and cancer patients often moves freely from one hospital to
31 another for different rounds of inpatient cancer care.²⁷ This makes it hard for clinicians in
32 leveraging different inpatient care episodes at different time points and hospitals into
33 continuous and synergetic service. Third, China has strong socio-cultural norms and
34 financial incentives that hinder cost control and guideline compliance.²⁸
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39 **Study aims**

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41 This study aims at identifying main pathways of RIC procedures for lung cancer patients
42 from rural Anhui, China and examining determinants of the pathways and economic
43 impacts. Specific questions to be addressed include: a) what combinations of diagnosis
44 and treatment procedures (or pathways for short) an individual patient may experience
45 during all his/her hospitalization episodes due to lung cancer-related problems; b) which
46 are the most and least frequent pathways; c) what determines the flow among these
47 pathways; d) which are the most and least cost-effective pathways in relation to the other
48 pathways; and e) what factors are associated with the relative cost-effectiveness.
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53 The above “pathways” of inpatient care means combinations of diagnosis and treatment
54 procedures an individual patient may experience during all his/her hospitalization
55 episodes due to lung cancer-related problems. Suppose a lung cancer patient experienced
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3 6 times/rounds of hospitalized care and during each of these hospitalization episodes, the
4 patient underwent several diagnosis and treatment procedures, all these procedures form
5 the “pathway” of this particular patient.
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8 **Methodology**

10 **Identification of procedures**

11 The study uses a self-designed and web-based data extraction form in identifying major
12 clinical procedures described in any RIC record under concern. The form lists all major
13 RIC procedures under two main domains, i.e., diagnostic procedures (e.g., chest X-ray,
14 chest CT, neck ultrasonography) and treatment procedures (e.g., surgical therapy,
15 chemotherapy, psycho-behavioral intervention).
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19 **Estimation of costs**

20 The study estimates overall and categorical costs (direct costs only) for each of the RIC
21 procedures (e.g., lung function examination, computed tomography, white blood cell
22 count) identified above using micro-costing techniques.^{29 30} Taking the example of lung
23 function examination, categorical costs include costs on personnel, equipment, materials,
24 regents and others needed in completing the examination; while overall cost of the
25 procedure equals the sum of all these categorical costs. In addition, the study also
26 calculates overall cost on individual inpatient by adding up the overall costs on all the
27 clinical procedures he/she has received.
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32 **Measurement of effectiveness**

33 The study uses both proximal variables of outcomes (PV) and ultimate outcome (UO)
34 measures of effectiveness of RIC procedures. The UO indicators derive from a follow up
35 survey about 2 years and half after the first hospitalization and include overall survival
36 (OS), progression-free survival (PFS), quality of life (QoL), and quality adjusted life
37 years (QALYs). Here, OoL is assessed using the widely recognized EQ-5D-5L
38 instrument.³¹
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42 The PV measures come from RIC records and include Eastern Cooperative Oncology
43 Group (ECOG), Karnofsky performance status (KPS) and compiled scores of: a)
44 symptoms (e.g., chronic cough, chest pain, wasting syndrome); b) lung functions (e.g.,
45 forced vital capacity, forced one second expiratory volume), c) image findings (e.g.,
46 number of nodules identified in the lung, size of the largest nodules, presence of pleura
47 or pericardial effusion). Each of these domain specific PV scores equals weighted sum of
48 all sub-indicators within the domain. For example, the compiled score of “lung functions”
49 equals the sum of weighted values of forced vital capacity, forced one second expiratory
50 volume etc. Here the weights come from the coefficients of multivariate regression
51 modeling using an UO indicator (e.g., OS) as the dependent variable; while forced vital
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3 capacity, forced one second expiratory volume etc. as the independent variables; and
4 stage of disease, age, gender and others as the confounding variables.
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6 **Calculation of cost-effectiveness**

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8 The study adopts relative cost-effectiveness ratios (RCERs) as the main indicators for
9 measuring cost-effectiveness. Here RCER is defined by the difference in cost between
10 two selected sets of RIC procedures, divided by the difference in their effect. More
11 specifically, $RCER = (C_{r+x} - C_r)/(E_{r+x} - E_r)$, where C_r and E_r is the cost and effect in
12 the reference group and C_{r+x} and E_{r+x} , the cost and effect in the group who have
13 underwent all the procedures in the reference group plus x, a specific procedure under
14 concern.³² Suppose, x represents a commonly used traditional Chinese medicine (TCM)
15 which incurs 100 dollars; while r, a typical combination of diagnosis and treatment
16 procedures without the TCM. The combination without the TCM costs 1000 dollars and
17 the survival time of patients who have adopted this combination is 1.5 years on average;
18 while the same figure for patients who have used the combination plus the TCM is 1.51.
19 Then the $C_{r+x} = 1000 + 100 = 1100$ dollars and the RCER of the TCM = $(1100-$
20 $100)/(1.51-1.5)=10000$ dollars per life year saved. Similarly, $RCER = (C_{r+x}/E_{r+x})/(C_r/$
21 $E_r) = (1100/1.51)/ (1000/1.50) = 1.09$.
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27 **Identification of influencing factors**

28 The study also extracts, from RIC records, data about patient factors commonly believed
29 to be linked with disease progression, treatment response and outcomes and utilization of
30 RIC procedures. These include: a) socio-demographics (e.g., age, gender, body height
31 and weight, education, employment, marital status, medical insurance); b) risk behaviors
32 and histories (e.g., smoking, alcohol drinking, history of cancer among family members);
33 c) historical and biological test findings (e.g., value of ALK, KRAS, EGFR, PDL1, CEA,
34 CA125, proGRP); d) comorbidities and complications (e.g., presence of superior vena
35 cava syndrome, brain metastases) and stage of disease. Here, disease staging uses TNM
36 system and this staging will be treated as the most important factor throughout the data
37 analysis especially in its effects on the flow of different pathways and their RCER.
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43 **Selection of participants**

44 The study is implemented in Anhui, an inland province located in middle and east China.
45 It has a population of 61.4 million and its per capita GDP and income rank in the middle
46 (the 14th) among all provinces in the nation.^{33 34} Its social, cultural and economic
47 background is representative of over 80% of the whole population in China.^{33 34} The
48 province has 68 rural counties and each of them divides into 10 to 20 townships.
49 Selection of participating counties, townships, patients and RIC case records uses a
50 clustered random sampling which proceeds in 5 steps. Step 1 classifies all the counties in
51 Anhui into southern, northern and middle areas. Step 2 randomly selects 3 counties from
52 each of these areas (12 counties in total). Step 3 randomly draws 4 townships from each
53 of the counties selected (48 townships in total). Step 4 searches the provincial
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3 reimbursement database of the New Rural Cooperative Medical System (NRCMS) and
4 identifies all the patients within the selected townships who had been first diagnosed with
5 primary lung cancer during July 1, 2014 and June 30, 2015. Step 5 searches the database
6 again for all episodes of hospitalization due to the lung cancer for the patients identified
7 in step 4. NRCMS covers 98% of the rural residents and the estimated number of patients
8 and admission episodes is about 5,000 and 25,000 respectively.
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11 The above sample size was determined by our study purpose of building multivariate
12 models of factors affecting the flow among and RCER of specific RIC pathways. Lung
13 cancer patients generally receive 4 to 6 rounds of inpatient care. Given the various
14 diagnostic and treatment procedures available, there are hundreds of potential RIC
15 pathways (combinations of diagnosis and treatment procedures from the first to the last
16 round of RIC). We plan to group these pathways into manageable (around 20) categories
17 depending on the resultant distribution of the actual pathways and we aim to enter 20-30
18 factors into the multivariate models for each of these categorical pathways. Based on
19 these pre-conditions and that the sample size of a multi-variable model should generally
20 be 10 times the number of independent variables, we need 250 patients for each pathway.
21 This translates into 5000 patients in total.
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26 27 **Data collection**

28 The study obtains data through follow-up survey and data extraction. The follow-up
29 survey applies to all the lung cancer patients identified above. It solicits information
30 about the patient's: a) disease progression (i.e., died, alive with or without progression);
31 b) if died, date of death; c) additional admissions due to the lung cancer not included in
32 the above mentioned NRCMS database. The survey uses a short structured questionnaire.
33 Administration of the questionnaire starts with a telephone interview (of the patient under
34 concern or his/her close relatives for up to 5 time attempts) followed by a face-to-face
35 interview (of the same respondents for up to 2 attempts) if the telephone contacts have
36 failed. The recruitment strives to reach over 85% rate of participation. And the
37 researchers are trained to record reasons of attrition for each of the patients they have lost
38 so as to allow for assessing potential biases. The data extraction applies to records of all
39 the hospital admission episodes identified via the NRCMS database and the follow up
40 survey. It uses a structured web-based form and extracts data about the clinical
41 procedures, costs, effectiveness and influencing factors described above. Two
42 experienced clinicians on care of lung cancer perform the data extraction. They visit (on
43 one-by-one base) all the relevant hospitals, ask for permission to examine the full records
44 and fill the worksheet independently first followed by discussions, if applicable, to solve
45 discrepancies.
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53 **Data analysis**

54 The data collected above allow a variety of descriptive and multivariate analysis
55 concerning the costs and effectiveness of RIC. The effectiveness analysis comprises all
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3 the UO indicators mentioned above including progression free survival, overall survival,
4 quality of life and DALYs. For each of these UO indicators, the analysis will produce: a)
5 estimation of average rates or values with 95% confidence intervals at different time
6 points after first diagnosis by disease stage, PV indicators, RIC pathways, non-hospital
7 care categories, age range etc.; b) multivariate regression models using similar variables
8 as independent variables; and c) path models using disease stage, RIC pathways, non-
9 hospital care categories, age range etc. as exogenous, complied PV indices as direct
10 endogenous, and individual PV indicators as indirect endogenous variables (Figure 1a).
11 Area under ROC (receiver operating characteristic) curve will be calculated for assessing
12 the predictability of models using binary classifier as the dependent variable (e.g.,
13 models of progression free survival, overall survival).
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18 The cost analysis explores mainly: a) Markov models of mean cost for managing lung
19 cancer patients (Figure 1b); b) overall and categorical costs on different rounds of
20 hospitalization by socio-demographic and selected clinical conditions (Figure 2); c)
21 scatter plot of RIC procedures using the occurrence rate and unit cost of individual
22 procedures as the coordinates; and d) multivariate regression models of overall and
23 selected categorical costs using disease stage, PV indicators, RIC pathways, non-hospital
24 care categories, age range etc. as independent variables.
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28 The cost-effectiveness analysis focuses primarily on constructing a pathway tree to help
29 estimate expected overall and pathway specific cost, effectiveness and identify pathways
30 with the highest or lowest RCER. The tree consists of different branches of combinations
31 of RIC procedures starting from the first to the last episode of inpatient care labeled with
32 estimated costs and possibilities along the pathways and outcomes at the end of the
33 pathways (Figure 3). Relevance of the pathway tree is tested by means of, for instance,
34 varying the percentage of patient flowing among the different pathways or the costs of
35 major diagnostic and treatment procedures consisting the braches and then examining
36 changes in the ranking of the pathways in terms of relative cost-effectiveness. The
37 analysis also pays particular attention to identifying as many as comparable pairs of RIC
38 pathways as possible and calculating RCER accordingly in a hope to uncover potential
39 pathways with practice, policy and research implications.
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45 The pathway tree construction will use TreeAge³⁵; while the descriptive and multi-
46 variate model analysis, SPSS 16. Cases with missing data about a specific item will be
47 excluded from the analysis involving the item and where applicable, the statistical null
48 hypothesis is be rejected at the significance level of $\alpha = 0.05$.
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51 **Ethics and dissemination**

52 The study protocol had been reviewed and approved by the Biomedical Ethics
53 Committee of Anhui Medical University (reference number: 20170312). Participation of
54 hospitals, patients and their relatives are voluntary and written informed consent is
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3 required for all participants. Findings from the study will be disseminated through
4 conventional academic routes such as peer-reviewed publications and presentations and
5 regional, national and international conferences.
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7 8 **Discussion** 9

10 The study would share the experience of lung cancer care from the rural Chinese
11 perspective. It is an important sharing of knowledge on population-based lung cancer
12 care, since most economic evidence comes from Europe and North America. In China,
13 traditional Chinese medicine is used to complement or replace western medicine. This
14 results in quite different pathways of lung cancer care that have seldom been well
15 explored in published literatures. China has a long history of almost no charges being
16 made for clinical consultations and most patients are used to paying only for medicines,
17 laboratory tests and equipment-based examinations. This forms a perverse financial
18 incentive for clinicians for ordering more sophisticated examinations and tests and for
19 over prescribing. China's lack of referral and follow up mechanisms also merits
20 particular attention. As an individual patient changes from one hospital (say for the first
21 round of treatment) to another (for the second round treatment), he/she may receive
22 different treatment regimens. Discontinued treatment and follow up may make it hard for
23 clinicians to base their treatment decisions on observed effects.
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30 Perhaps the most noteworthy findings of the current study may be the description of the
31 pathways of RIC procedures and their economic impacts (Figure 2). These pathways will
32 provide easily understandable means for estimating and identifying, among others, the
33 following: a) which pathways or combinations of procedures happen most or least in
34 routine practice during different rounds of hospitalization for inpatients suffering from
35 lung cancer in rural China; b) which pathways (from the first to last round of
36 hospitalization) incur the highest or lowest direct costs; and c) which pathways result in
37 the best or worst patient outcome in terms of different UO measures. These have
38 important implications for clinical decision-making as well as policy-making.
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42 Another point worth mentioning in particular refers to the links between the domain
43 specific proximate (PV) indices to key ultimate outcome (UO) indicators (e.g., OS, PFS,
44 QALYs) generated via a large scale (involving 5000 lung cancer patients) retrospective
45 cohort study. They provide useful references for clinicians on care of lung cancer patients
46 in selecting appropriate procedures to achieve optimal collective contributions to UO.³⁶
47 At present, although PV indicators are observed routinely, they are presented to
48 clinicians as individual indicators rather than compiled indices. And given the large
49 number of PV indicators involved and the complex relations between RIC procedures
50 and PV indicators and then UO indicators, it is difficult for practicing clinicians to make
51 balanced decisions upon their personal experiences.³⁷
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3 In addition, this study addresses RIC for lung cancer at hospitals in China from a range
4 of meaningful perspectives. The study reinforces the concepts introduced in the landmark
5 studies of Fisher et al and Wennberg et al, which convincingly demonstrated that high
6 quality was not necessarily associated with high cost.³⁸ Describing inpatient lung cancer
7 care in a view that its value is directly proportional to outcomes and inversely
8 proportional to costs helps in guiding quality improvement by either better outcomes
9 and/or lower costs.³⁹ The study calculates and compares the collective costs and
10 effectiveness of different RIC pathways as a whole and thus informs coordinated
11 inpatient care episodes and procedures at different time points and hospitals. The study
12 enables RCER estimation for specific guideline recommended procedures (GRPs) using
13 various combinations of real and uncontrollable RIC procedures as the reference and thus
14 enhances understanding and application of GRPs established through well-controlled
15 studies in routine practice contexts.
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21 The study also has limitations. The first limit concerns data reliability. Although the
22 majority of data are extracted from RIC records kept at hospitals, the study uses self-
23 reported data about quality of life and inpatient, outpatient and home care. Self-reports
24 are prone to various biases including recall problems particularly among the elderly, over
25 or under reporting by the respondents for reasons like perceived expectations from the
26 researchers or for fearing of potential worries or distress. These biases may be reduced to
27 a minimum in our study by means of interviewer training, use of chorological recall and
28 probing techniques, and cross-checks of findings from patient interviews, health
29 insurance database and hospital records. More importantly, the study uses EQ-5D-5L in
30 assessing quality of life. It has already been tested with adequate reliability both
31 internationally and in China. Regarding non-hospitalized care, the study asks only simple
32 questions about what kind of care the patients have experienced and when and for how
33 long. These questions are relatively memorable and easy to answer. The second limit
34 relates to selective study content. The study considers only inpatient care; while patients
35 may use various self-treatment and outpatient treatment in addition to inpatient care.^{40 41}
36 Inpatient and non-inpatient treatment may substitute each other to some extent. These
37 may result in under-estimation of the effectiveness of RIC procedures. Fortunately, this
38 under-estimation may be offset to a large extent by treating non-hospital care as
39 confounders and the study data to be collected allow this exercise. Third, the study
40 considers only direct costs rather than full costs taking both direct and indirect costs into
41 consideration. In addition, different hospitals use different equipment, reagents and
42 medicines. Their quality of case records may also vary substantially. These raise
43 compatibility concerns in pooling data from different hospitals together and performing
44 aggregate analysis. Finally, readers may raise concerns about representativeness of
45 inpatients to the larger cancer patients. Hospitalization rates documented from other
46 countries vary greatly;⁴² while similar data from China are scarce. Our estimation, using
47 the dataset of the last province-wide Household Health Survey of Anhui, of the
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3 proportion of lung cancer patients who had been admitted to hospitals at least once was
4 as high as 89%.⁴³
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6 7 **Competing interests**

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9 The authors declare no competing interests.
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11 12 **Authors' contributions**

13
14 XS and MD contributed equally in conceiving this project, facilitating protocol and
15 instrument development, and drafting this manuscript. RF, ML, PZ and TJ are kore
16 researchers for cost estimation, record extraction, follow up survey and data analysis
17 respectively. DW provided expertise for overall design of the study, and revised and
18 finalized the manuscript. All authors have read and approved the final submission.
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27 University, Anhui and Luan Center for Diseases Control and Prevention.
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3 Figure 1 Schematic structure of sample multivariate models to be built
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5 Figure 2 Simulated cost by selected socio-demographics and clinical characteristics
6 (TC=total cost; KRMB=1000 Chinese yuan)
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8 Figure 3 Anticipated “procedure-outcome” tree of inpatient lung cancer care (Tx = the xth
9 round of hospitalization; Cx = the xth combination of clinical procedures; Px = possibility
10 of using the xth combinations of clinical procedures; Ox = the xth patient outcome
11 index/indicator)
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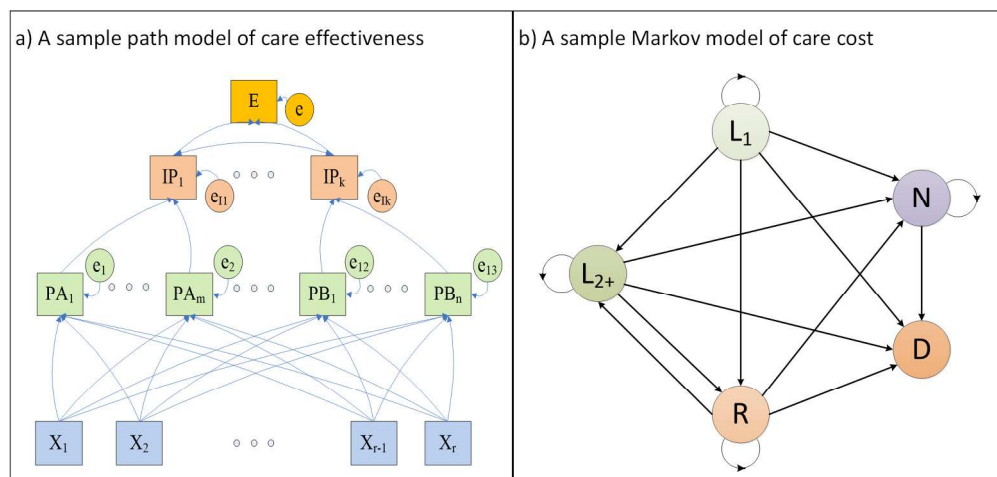


Figure 1 Schematic structure of sample multivariate models to be built/ X=independent variables; PA or PB=domain A or proximate indicators of effectiveness; IP=index of proximate variables; e=systematic error; and E= effectiveness, e.g., overall survival, QALYs; L₁=first line treatment; L₂₊=second or third line treatment; R=remission; N=no active treatment; D=death.

188x88mm (300 x 300 DPI)

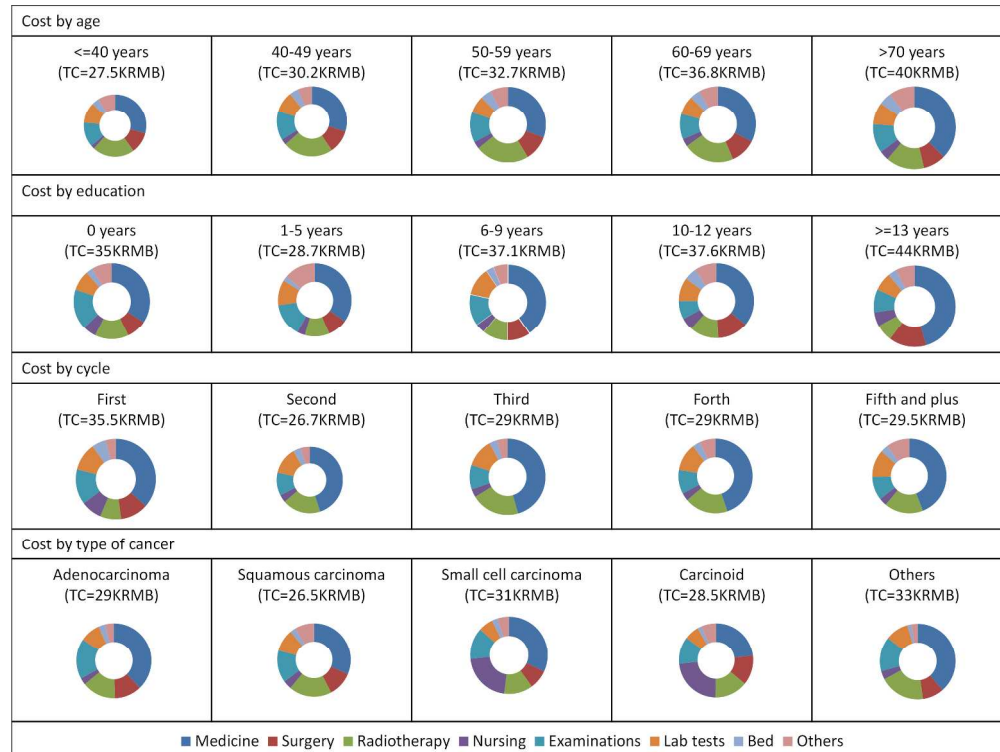


Figure 2 Simulated cost by selected socio-demographics and clinical characteristics (TC=total cost; KRMB=1000 Chinese yuan)

249x187mm (300 x 300 DPI)

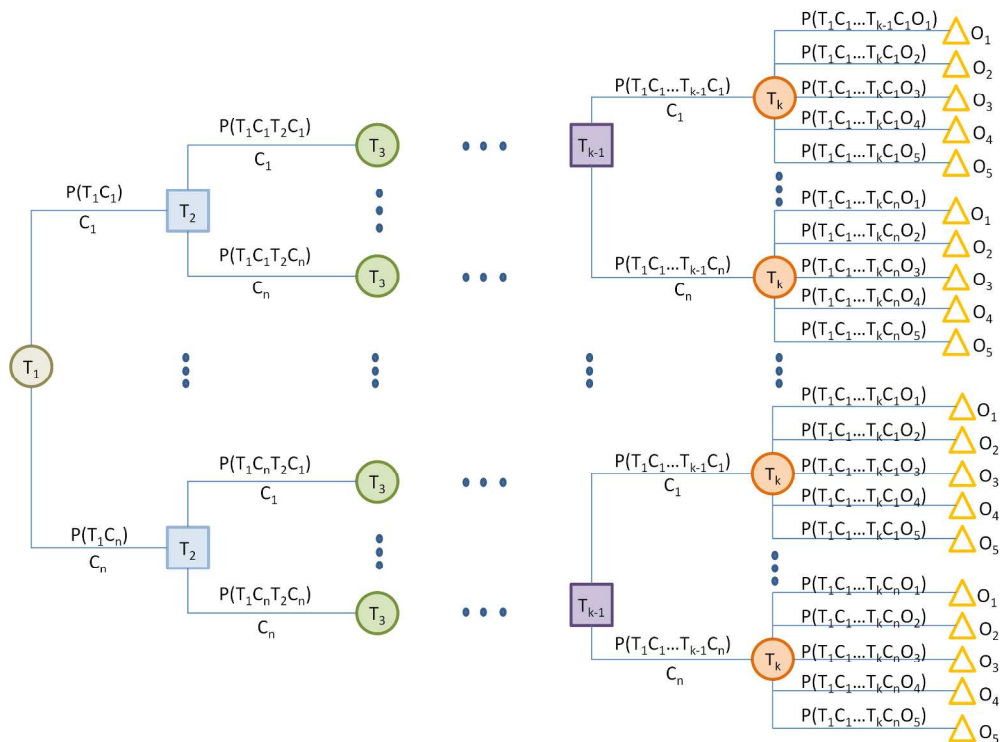


Figure 3 Anticipated "procedure-outcome" tree of inpatient lung cancer care (T_x = the x^{th} round of hospitalization; C_x = the x^{th} combination of clinical procedures; P_x = possibility of using the x^{th} combinations of clinical procedures; O_x = the x^{th} patient outcome index/indicator)

242x183mm (300 x 300 DPI)

BMJ Open

Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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Pathways and cost-effectiveness of routine lung cancer inpatient care in rural Anhui, China: a retrospective cohort study protocol

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ABSTRACT

Introduction: Routine inpatient care (RIC) for cancer patients forms various pathways of clinical procedures. Although most individual procedures comprising the pathways have been tested via clinical trials, little is known about the collective cost and effectiveness of the pathways as a whole. This study aims at exploring RIC pathways for lung cancer patients from rural Anhui, China and their determinants and economic impacts.

Methods and analysis: The study adopts a retrospective cohort design and proceeds in 5 steps. Step 1 defines 4 main categories of study variables including clinical procedures, direct cost and effectiveness of procedures, and factors affecting use of these procedures and their cost and effectiveness. Step 2 selects a cohort of 5000 lung cancer patients diagnosed between July 1, 2014 and June 30, 2015 from rural Anhui by clustered-random sampling. Step 3 retrieves the records of all the inpatient care episodes due to the lung cancer and extracts data about RIC procedures, proximate variables (e.g., Karnofsky performance status, lung function score) of patient outcomes and related factors (e.g., stage of cancer, age, gender) by 2 independent clinician researchers using a web-based form. Step 4 estimates the direct cost of each of the RIC procedures using micro-costing and collects data about ultimate patient outcomes (survival and progression-free survival) through a follow up survey of patients and/or their close relatives. Step 5 analyzes data collected and explores pathways of RIC procedures and their relations with patient outcomes, costs, cost-effect ratios and a whole range of clinical and socio-demographic factors using multivariate regression and path models.

Ethics and dissemination: The study protocol has been approved by authorized ethics committee of Anhui Medical University (reference number: 20170312). Findings from the study will be disseminated through conventional academic routes such as peer-reviewed publications and presentations at regional, national and international conferences.

Trial registry

ISRCTN25595562

Key words: cost effectiveness, lung cancer, inpatient care, retrospective study, China

Strengths and limitations of this study

- The study adopts a retrospective cohort study design involving a large representative sample of community patients;
- It provides data for determining the cost-effectiveness of different treatment approaches as a whole rather than individual procedures;
- It informs our understanding of routine inpatient lung cancer care for rural Chinese, a huge yet understudied population;
- It extracts data from routine records kept at different hospitals and thus suffers from discrepancies in performances and data qualities.

Introduction

Lung cancer has been the most common cancer in the world for several decades.¹ Estimated new cases of the disease was 1.8 million in 2012 (12.9% of all cancers), 58% of which occurred in less developed regions. It was also the most common cause of death from cancer worldwide, being responsible for nearly one in five (1.59 million in absolute number) of the total.² In China, lung cancer incidence displayed a slight decreasing trend in the past few years, particularly for males. However, it is still the top first cancer for males and second for females, accounting for 25.2% of all new cancer cases and 29.5% of all cancer deaths in 2012.³

Routine inpatient care (RIC) for lung cancer consists of a combination of procedures. Patients with possible lung cancer need a detailed history and physical examination first. Then they should undergo posterior-anterior and lateral chest radiographs as well as CT scans of the chest and abdomen. In order to further confirm and determine stage and histology of the lesion, other diagnostic methods needed include whole-body fluoro-deoxy-glucose positron emission tomography, endoscopic ultrasound, sputum cytology, fine-needle aspiration, bronchoscopy etc. Following diagnosis of lung cancer, the patients proceed with combined-modality therapies depending on stage of the disease and co-morbidities and complications. Historically, surgery provides the best chance for cure for patients whose lung cancers are limited to the hemithorax and can be totally encompassed by excision.^{4 5} Surgery has been generally used in combination with external-beam radiotherapy for control of the primary tumor and regional lymphatics.⁶ In addition, chemotherapy has also been advocated as an integral part of combined modality approaches to earlier stages of disease.^{7 8} For unselected advanced none-small cell lung cancer, platinum-based combinations have become the standard of care; while cisplatin- or carboplatin-based doublets are standard for patients with stage IV disease.^{9 10} More recently, EGFR tyrosine kinase inhibitors have been introduced in second- and third-line treatment of advanced disease and in first-line treatment for selected patients.¹¹

Given the complex procedures, ensuring quality RIC for lung cancer patients has been most challenging and guidelines are widely used in addressing this challenge. Numerous

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3 studies have documented positive relations between compliance with guidelines and
4 patient outcomes.^{12 13} However, researchers have also raised concerns about guidelines.
5 One of such concerns refers to lack of adequate consideration of costs. Most clinical
6 procedures not only affect disease outcomes but also incur considerable costs.^{14 15} Yet
7 guidelines are based on trials focused primarily on effectiveness (e.g., survival) with little
8 attention being paid to economic consequences.¹⁶ Another concern relates to
9 incompatible population between clinical trials and RIC. Clinical trials on which
10 guidelines are based use highly selective populations; while RIC serves a general lung
11 cancer population with different age, performance status and comorbidities.^{17 18} A third
12 concern revolves uncertain interactions between procedures. Although most individual
13 guideline recommended procedures (GRPs) have established evidences, they are not used
14 in isolation but in conjunction with others forming various clinical combinations. Efforts
15 systematically assessing and comparing these combinations are scarce.¹⁹⁻²² A fourth
16 concern originates from varied compliance with guidelines since RIC often deviates
17 substantially from guidelines.^{23 24} The cost-effectiveness of these “substandard” or mixed
18 combinations of procedures (partly from guidelines, partly from experiences of
19 individual clinicians) falls far from well-understood.²⁵ These all point to a clear need for
20 evaluating RIC even though guidelines are widely available.
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27 All the above concerns are most pertinent to China. First, China has a unique “dual”
28 medical care system in which patients often receive western medicine and traditional
29 Chinese medicine simultaneously or in turn.²⁶ Second, China lacks coordinated referral
30 and follow up mechanisms and cancer patients often moves freely from one hospital to
31 another for different rounds of inpatient cancer care.²⁷ This makes it hard for clinicians in
32 leveraging different inpatient care episodes at different time points and hospitals into
33 continuous and synergetic service. Third, China has strong socio-cultural norms and
34 financial incentives that hinder cost control and guideline compliance.²⁸
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39 **Study aims**

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42 This study aims at identifying main pathways of RIC procedures for lung cancer patients
43 from rural Anhui, China and exploring determinants of the pathways and their economic
44 impacts. Specific questions to be addressed include: a) what combinations of diagnosis
45 and treatment procedures (or pathways for short) an individual patient may experience
46 during all his/her hospitalization episodes due to lung cancer-related problems; b) which
47 are the most and least frequent pathways; c) what determines the flow among these
48 pathways; d) which are the most and least cost-effective pathways in relation to the other
49 pathways; and e) what factors are associated with the relative cost-effectiveness.
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53 The above “pathways” of inpatient care means combinations of diagnosis and treatment
54 procedures an individual patient may experience during all his/her hospitalization
55 episodes due to lung cancer-related problems. Suppose a lung cancer patient experienced
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3 6 times/rounds of hospitalized care and during each of these hospitalization episodes, the
4 patient underwent several diagnosis and treatment procedures, all these procedures form
5 the “pathway” of this particular patient. It is worth noting that findings of the cost-
6 effectiveness analysis are exploratory rather than implying that they are of sufficient robustness
7 to be used to inform policy changes.
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10 **Methodology**

11 **Identification of procedures**

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13 The study uses a self-designed and web-based data extraction form in identifying major
14 clinical procedures described in any RIC record under concern. The form lists all major
15 RIC procedures under two main domains, i.e., diagnostic procedures (e.g., chest X-ray,
16 chest CT, neck ultrasonography) and treatment procedures (e.g., surgical therapy,
17 chemotherapy, psycho-behavioral intervention).
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22 **Estimation of costs**

23 The study estimates overall and categorical costs (direct costs only) for each of the RIC
24 procedures (e.g., lung function examination, computed tomography, white blood cell
25 count) identified above using micro-costing techniques.^{29 30} Taking the example of lung
26 function examination, categorical costs include costs on personnel, equipment, materials,
27 regents and others needed in completing the examination; while overall cost of the
28 procedure equals the sum of all these categorical costs. In addition, the study also
29 calculates grand total cost on individual inpatient by adding up the overall costs on all the
30 clinical procedures he/she has received.
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35 **Measurement of effectiveness**

36 The study uses both proximal variables of outcomes (PV) and ultimate outcome (UO)
37 measures of effectiveness of RIC procedures. The UO indicators derive from a follow up
38 survey about 2 years and half after the first hospitalization and include overall survival
39 (OS), progression-free survival (PFS), quality of life (QoL), and quality adjusted life
40 years (QALYs). Here, QoL is assessed using the widely recognized EQ-5D-5L
41 instrument.³¹
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45 The PV measures come from RIC records and include Eastern Cooperative Oncology
46 Group (ECOG), Karnofsky performance status (KPS) and compiled scores of: a)
47 symptoms (e.g., chronic cough, chest pain, wasting syndrome); b) lung functions (e.g.,
48 forced vital capacity, forced one second expiratory volume), c) image findings (e.g.,
49 number of nodules identified in the lung, size of the largest nodules, presence of pleura
50 or pericardial effusion). Each of these domain specific PV scores equals weighted sum of
51 all sub-indicators within the domain. For example, the compiled score of “lung functions”
52 equals the sum of weighted values of forced vital capacity, forced one second expiratory
53 volume etc. Here the weights come from the coefficients of multivariate regression
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3 modeling using an UO indicator (e.g., OS) as the dependent variable; while forced vital
4 capacity, forced one second expiratory volume etc. as the independent variables; and
5 stage of disease, age, gender and others as the confounding variables.
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7 **Calculation of cost-effectiveness**

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9 The study adopts relative cost-effectiveness ratios (RCERs) as the main indicators for
10 measuring cost-effectiveness. Here RCER is defined by the difference in cost between
11 two selected sets of RIC procedures, divided by the difference in their effectiveness.
12 More specifically, $RCER = (C_{r+x} - C_r)/(E_{r+x} - E_r)$, where C_r and E_r is the cost and
13 effectiveness in the reference group and C_{r+x} and E_{r+x} , the cost and effectiveness in the
14 group who have underwent all the procedures in the reference group plus x, a specific
15 procedure under concern.³² Suppose, x represents a commonly used traditional Chinese
16 medicine (TCM) which incurs 100 dollars; while r, a typical combination of diagnosis
17 and treatment procedures without the TCM. The combination without the TCM costs
18 1000 dollars and the survival time of patients who have adopted this combination is 1.5
19 years on average; while the same figure for patients who have used the same combination
20 plus the TCM is 1.51. Then the $C_{r+x} = 1000 + 100 = 1100$ dollars and the RCER of
21 the TCM = $(1100-100)/(1.51-1.5)=10000$ dollars per life year saved. Similarly, $RCER =$
22 $(C_{r+x}/E_{r+x})/(C_r/E_r) = (1100/1.51)/(1000/1.50) = 1.09$.
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28 **Identification of influencing factors**

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30 The study also extracts, from RIC records, data about patient factors commonly believed
31 to be linked with disease progression, treatment response and outcomes and utilization of
32 RIC procedures. These include: a) socio-demographics (e.g., age, gender, body height
33 and weight, education, employment, marital status, medical insurance); b) risk behaviors
34 and histories (e.g., smoking, alcohol drinking, history of cancer among family members);
35 c) historical and biological test findings (e.g., value of ALK, KRAS, EGFR, PDL1, CEA,
36 CA125, proGRP); d) comorbidities and complications (e.g., presence of superior vena
37 cava syndrome, brain metastases) and stage of disease. Here, disease staging uses TNM
38 system and this staging will be treated as the most important factor throughout the data
39 analysis especially in its effects on the flow of different pathways and their RCER.
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44 **Selection of participants**

45 The study is implemented in Anhui, an inland province located in middle and east China.
46 It has a population of 61.4 million and its per capita GDP and income rank in the middle
47 (the 14th) among all provinces in the nation.^{33 34} Its social, cultural and economic
48 background is representative of over 80% of the whole population in China.^{33 34} The
49 province has 68 rural counties and each of them divides into 10 to 20 townships.
50 Selection of participating counties, townships, patients and RIC case records uses a
51 clustered random sampling which proceeds in 5 steps. Step 1 classifies all the counties in
52 Anhui into southern, northern and middle areas. Step 2 randomly selects 3 counties from
53 each of these areas (12 counties in total). Step 3 randomly draws 4 townships from each
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of the counties selected (48 townships in total). Step 4 searches the provincial reimbursement database of the New Rural Cooperative Medical System (NRCMS) and identifies all the patients within the selected townships who had been first diagnosed with primary lung cancer during July 1, 2015 and June 30, 2016. Step 5 searches the database again for all episodes of hospitalization due to the lung cancer for the patients identified in step 4. NRCMS covers 98% of the rural residents and the estimated number of patients and admission episodes is about 5,000 and 25,000 respectively.

The above sample size was determined by our study purpose of building multivariate models of factors affecting the flow among and RCER of specific RIC pathways. Lung cancer patients generally receive 4 to 6 rounds of inpatient care. Given the various diagnostic and treatment procedures available, there are hundreds of potential RIC pathways (combinations of diagnosis and treatment procedures from the first to the last round of RIC). We plan to group these pathways into manageable (around 20) categories depending on the resultant distribution of the actual pathways and we aim to enter 20-30 factors into the multivariate models for each of these categorical pathways. Based on these pre-conditions and that the sample size of a multi-variable model should generally be 10 times the number of independent variables, we need 250 patients for each pathway. This translates into 5000 patients in total.

Data collection

The study obtains data through follow-up survey and data extraction. The follow-up survey applies to all the lung cancer patients identified above. It solicits information about the patient's: a) disease progression (i.e., died, alive with or without progression); b) if died, date of death; c) additional admissions due to the lung cancer not included in the above mentioned NRCMS database. The survey uses a short structured questionnaire. Administration of the questionnaire starts with a telephone interview (of the patient under concern or his/her close relatives for up to 5 time attempts) followed by a face-to-face interview (of the same respondents for up to 2 attempts) if the telephone contacts have failed. The recruitment strives to reach over 85% rate of participation. The researchers are trained to record reasons of attrition for each of the patients they have lost so as to allow for assessing potential biases. The data extraction applies to records of all the hospital admission episodes identified via the NRCMS database and the follow up survey. It uses a structured web-based form and extracts data about the clinical procedures, costs, effectiveness and influencing factors described above. Two experienced clinicians on care of lung cancer perform the data extraction. They visit (on one-by-one base) all the relevant hospitals, ask for permission to examine the full records and fill the worksheet independently first followed by discussions, if applicable, to solve discordances.

Data analysis

The data collected above allow a variety of descriptive and multivariate analysis concerning the costs and effectiveness of RIC. The effectiveness analysis comprises all

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3 the UO indicators including progression free survival, overall survival, quality of life and
4 DALYs. For each of these UO indicators, the analysis will produce: a) estimation of
5 average rates or values with 95% confidence intervals at different time points after first
6 diagnosis by disease stage, PV indicators, RIC pathways, non-hospital care categories,
7 age range etc.; b) multivariate regression models using similar variables as independent
8 variables; and c) path models using disease stage, RIC pathways, non-hospital care
9 categories, age range etc. as exogenous, complied PV indices as direct endogenous, and
10 individual PV indicators as indirect endogenous variables (Figure 1a). Area under ROC
11 (receiver operating characteristic) curve will be estimated for assessing the predictability
12 of models using binary classifier as the dependent variable (e.g., models of progression
13 free survival, overall survival).
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18 The cost analysis explores mainly: a) Markov models of mean cost for managing lung
19 cancer patients (Figure 1b); b) overall and categorical costs on different rounds of
20 hospitalization by socio-demographic and selected clinical conditions (Figure 2); c)
21 scatter plot of RIC procedures using the occurrence rate and unit cost of individual
22 procedures as the coordinates; and d) multivariate regression models of overall and
23 selected categorical costs using disease stage, PV indicators, RIC pathways, non-hospital
24 care categories, age range etc. as independent variables.
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28 The cost-effectiveness analysis focuses primarily on constructing a pathway tree to help
29 estimate expected overall and pathway specific cost, effectiveness and identify pathways
30 with the highest or lowest RCER. The tree consists of different branches of combinations
31 of RIC procedures starting from the first to the last episode of inpatient care labeled with
32 estimated costs and possibilities along the pathways and outcomes at the end of the
33 pathways (Figure 3). Relevance of the pathway tree is tested by means of, for instance,
34 varying the percentage of patient flowing among the different pathways or the costs of
35 major diagnostic and treatment procedures consisting the braches and then examining
36 changes in the ranking of the pathways in terms of relative cost-effectiveness. The
37 analysis also pays particular attention to identifying as many as comparable pairs of RIC
38 pathways as possible and calculating RCER accordingly in a hope to uncover potential
39 pathways of practice, policy and research implications.
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45 The pathway tree construction will use TreeAge³⁵; while the descriptive and multi-
46 variate model analysis, SPSS 16. Cases with missing data about a specific item will be
47 excluded from the analysis involving the item and where applicable, the statistical null
48 hypothesis is be rejected at the significance level of $\alpha = 0.05$.
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51 **Ethics and dissemination**

52 The study protocol had been reviewed and approved by the Biomedical Ethics
53 Committee of Anhui Medical University (reference number: 20170312). Participation of
54 hospitals, patients and their relatives are voluntary and written informed consent is
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3 required for all participants. Findings from the study will be disseminated through
4 conventional academic routes such as peer-reviewed publications and presentations and
5 regional, national and international conferences.
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8 **Discussion**

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10 The study would share the experience of lung cancer care from the rural Chinese
11 perspective. It is an important sharing of knowledge on population-based lung cancer
12 care, since most economic evidence comes from Europe and North America. In China,
13 traditional Chinese medicine is used to complement or replace western medicine. This
14 results in quite different pathways of lung cancer care that have seldom been well
15 explored in published literatures. China has a long history of almost no charges being
16 made for clinical consultations and most patients are used to paying only for medicines,
17 laboratory tests and equipment-based examinations. This forms a perverse financial
18 incentive for clinicians to order more sophisticated examinations and tests and to over
19 prescribing. China's lack of referral and follow up mechanisms also merits particular
20 attention. As an individual patient changes from one hospital (say for the first round of
21 treatment) to another (for the second round treatment), he/she may receive different
22 treatment regimens. Discontinued treatment and follow up may make it hard for
23 clinicians to base their treatment decisions on observed effects.
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30 Perhaps the most noteworthy findings of the current study may be the description of the
31 pathways of RIC procedures and their economic impacts (Figure 2). These pathways will
32 provide easily understandable means for estimating and identifying, among others, the
33 following: a) which pathways or combinations of procedures happen most or least in
34 routine practice during different rounds of hospitalization for inpatients suffering from
35 lung cancer in rural China; b) which pathways (from the first to last round of
36 hospitalization) incur the highest or lowest direct costs; and c) which pathways result in
37 the best or worst patient outcome in terms of different UO measures. These have
38 important implications for clinical decision-making as well as policy-making.
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43 Another point worth mentioning refers to the links between the domain specific
44 proximate (PV) indices to key ultimate outcome (UO) indicators (e.g., OS, PFS, QALYs)
45 generated via a large scale (involving 5000 lung cancer patients) retrospective cohort
46 study. They provide useful information for clinicians on care of lung cancer patients in
47 selecting appropriate procedures to achieve optimal collective contributions to UO.³⁶ At
48 present, although PV indicators are observed routinely, they are presented to clinicians as
49 individual indicators rather than compiled indices. Given the large number of PV
50 indicators involved and the complex relations between RIC procedures and PV indicators
51 and then UO indicators, it is difficult for practicing clinicians to make balanced decisions
52 upon their personal experiences.³⁷
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3 In addition, this study addresses RIC for lung cancer at hospitals in China from a range
4 of meaningful perspectives. The study reinforces the concepts introduced in the landmark
5 studies of Fisher et al and Wennberg et al, which convincingly demonstrated that high
6 quality was not necessarily associated with high cost.³⁸ Describing inpatient lung cancer
7 care in a view that its value is directly proportional to outcomes and inversely
8 proportional to costs helps in guiding quality improvement by either better outcomes
9 and/or lower costs.³⁹ The study calculates and compares the collective costs and
10 effectiveness of different RIC pathways as a whole and thus informs coordinated
11 inpatient care episodes and procedures at different time points and hospitals. The study
12 enables RCER estimation for specific guideline recommended procedures (GRPs) using
13 various combinations of real and uncontrolled RIC procedures as the reference and thus
14 enhances understanding and application of GRPs established through well-controlled
15 studies.
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21 The study also has limitations. The first limitation concerns data reliability. Although the
22 majority of data are extracted from RIC records kept at hospitals, the study uses self-
23 reported data about quality of life and inpatient, outpatient and home care. Self-reports
24 are prone to various biases including recall problems particularly among the elderly, over
25 or under reporting by the respondents for reasons like perceived expectations from the
26 researchers or for fearing of potential worries or distress. These biases may be reduced to
27 a minimum in our study by means of interviewer training, use of chorological recall and
28 probing techniques, and cross-checks of findings from patient interviews, health
29 insurance database and hospital records. More importantly, the study uses EQ-5D-5L in
30 assessing quality of life. It has already been tested with adequate reliability both
31 internationally and in China. Regarding non-hospitalized care, the study asks only simple
32 questions about what kind of care the patients have experienced and when and for how
33 long. These questions are relatively memorable and easy to answer. The second
34 limitation relates to selective study content. The study considers only inpatient care;
35 while patients may use various self-treatment and outpatient treatment in addition to
36 inpatient care.^{40 41} Inpatient and non-inpatient treatment may substitute each other to
37 some extent. These may result in under-estimation of the effectiveness of RIC procedures.
38 Fortunately, this under-estimation may be offset to a large extent by treating non-hospital
39 care as confounders and the study data to be collected allow this exercise. Third, the
40 study considers only direct costs rather than full costs taking both direct and indirect
41 costs into consideration. In addition, different hospitals use different equipment, reagents
42 and medicines. Their quality of records may also vary substantially. These raise
43 compatibility concerns in pooling data from different hospitals together and performing
44 aggregate analysis. Finally, readers may raise concerns about representativeness of
45 inpatients to the larger cancer patients. Hospitalization rates documented from other
46 countries varied greatly,⁴² while similar data from China are scarce. Our estimation,
47 using the dataset of the last province-wide Household Health Survey of Anhui, of the
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3 proportion of lung cancer patients who had been admitted to hospitals at least once was
4 as high as 89%.⁴³
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6 7 **Competing interests**

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9 The authors declare no competing interests.
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11 12 **Authors' contributions**

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14 XS and MD contributed equally in conceiving this project, facilitating protocol and
15 instrument development, and drafting this manuscript. RF, ML, PZ and TJ are kore
16 researchers for cost estimation, record extraction, follow up survey and data analysis
17 respectively. DW provided expertise for overall design of the study, and revised and
18 finalized the manuscript. All authors have read and approved the final submission.
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27 University, Anhui and Luan Center for Diseases Control and Prevention.
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3 Figure 1 Schematic structure of sample multivariate models to be built
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5 Figure 2 Simulated cost by selected socio-demographics and clinical characteristics
6 (TC=total cost; KRMB=1000 Chinese yuan)
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8 Figure 3 Anticipated “procedure-outcome” tree of inpatient lung cancer care (Tx = the xth
9 round of hospitalization; Cx = the xth combination of clinical procedures; Px = possibility
10 of using the xth combinations of clinical procedures; Ox = the xth patient outcome
11 index/indicator)
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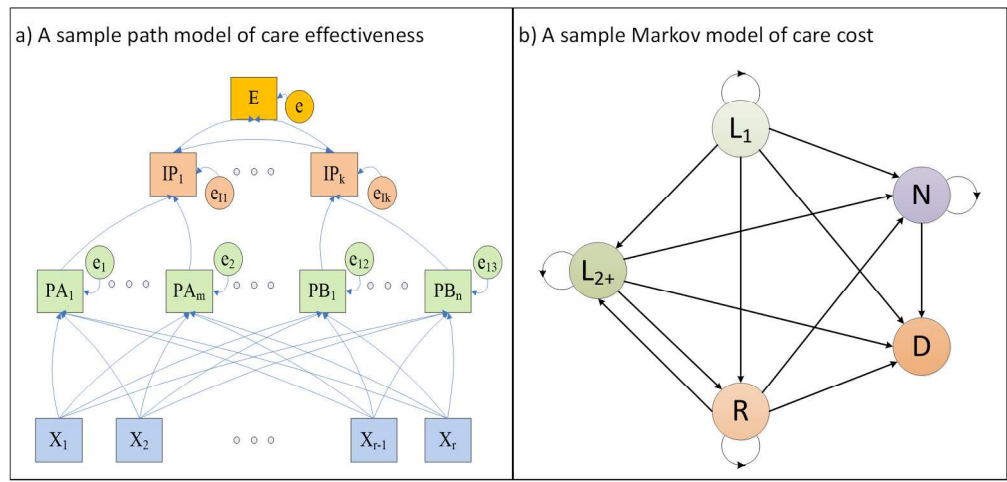


Figure 1 Schematic structure of sample multivariate models to be built/ X=independent variables; PA or PB=domain A or proximate indicators of effectiveness; IP=index of proximate variables; e=systematic error; and E= effectiveness, e.g., overall survival, QALYs; L₁=first line treatment; L₂₊=second or third line treatment; R=remission; N=no active treatment; D=death.

188x88mm (300 x 300 DPI)

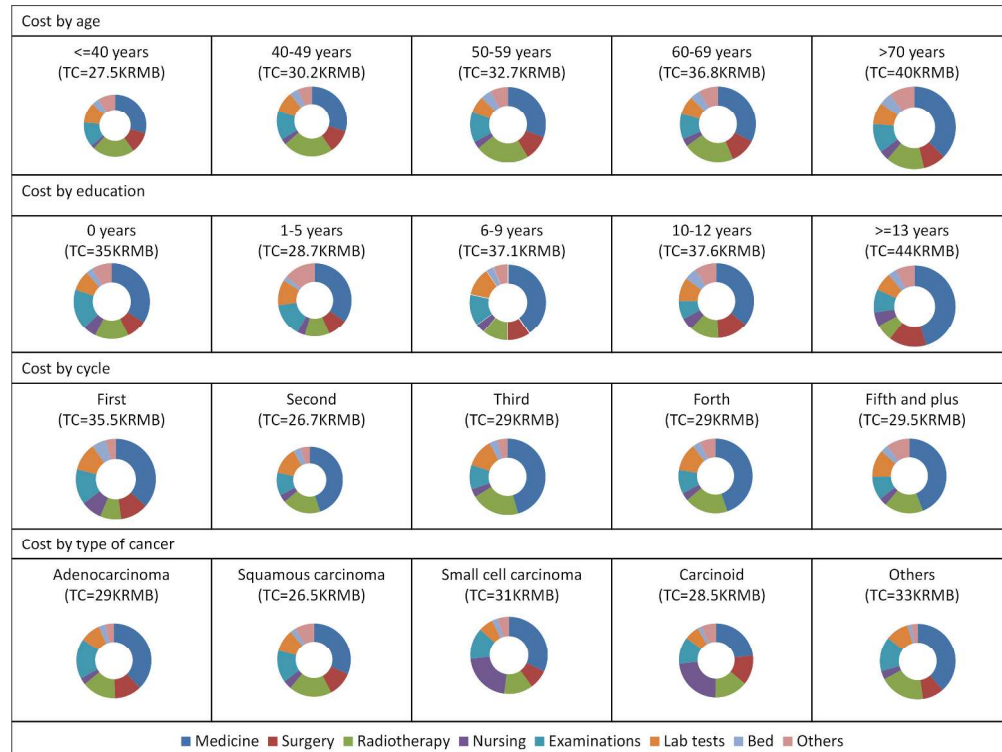


Figure 2 Simulated cost by selected socio-demographics and clinical characteristics (TC=total cost; KRMB=1000 Chinese yuan)

249x187mm (300 x 300 DPI)

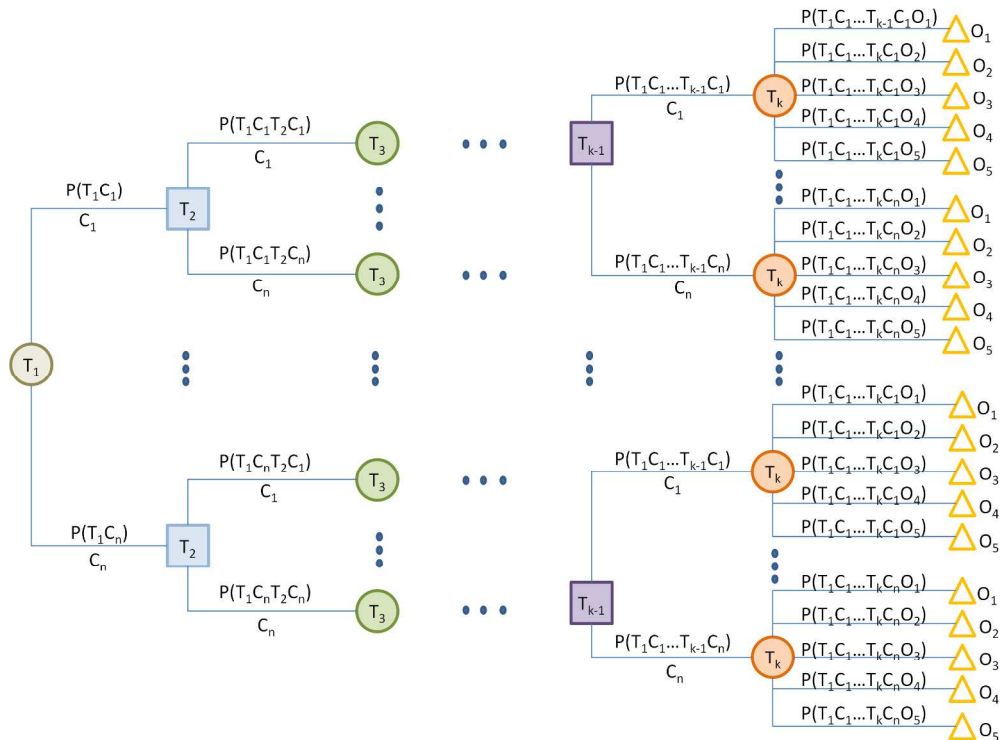


Figure 3 Anticipated "procedure-outcome" tree of inpatient lung cancer care (T_x = the x^{th} round of hospitalization; C_x = the x^{th} combination of clinical procedures; P_x = possibility of using the x^{th} combinations of clinical procedures; O_x = the x^{th} patient outcome index/indicator)

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BMJ Open

Is it feasible to conduct a randomised controlled trial of pre-transplant exercise (pre-habilitation) for multiple myeloma patients awaiting autologous haematopoietic stem cell transplantation? (PREEMPT study).

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5 **Title:** **Is it feasible to conduct a randomised controlled trial of**
6 **pre-transplant exercise (pre-habilitation) for multiple**
7 **myeloma patients awaiting autologous haematopoietic**
8 **stem cell transplantation? (PREeMPT study).**
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ABSTRACT

Introduction:

While myeloma is an incurable malignancy, developments in disease management have led to increased life expectancy in recent years. Treatment typically involves stem-cell transplantation. Increased survival rates equates to more patients living with the burden of both the disease and its treatment for increasing numbers of years, rendering myeloma a long term condition.

Evidence exists to demonstrate the benefits of exercise for patients recovering from stem cell transplantation, and pre-habilitation – exercise before treatment - has been shown to be effective in other disease areas. To date there has been no research into pre-habilitation in myeloma patients awaiting transplantation treatment.

Our objective is to determine whether it is feasible to conduct a randomised controlled trial into pre-transplant exercise for patients with multiple myeloma who are awaiting autologous stem cell transplantation.

Methods and analysis:

This mixed methods study identifies patients with diagnosis of multiple myeloma who have been assigned to the autologous transplantation list and invites them to participate in 6 weekly sessions of individualised, supervised exercise whilst awaiting transplantation.

Quantitative data to determine feasibility targets include rates of recruitment, adherence and adverse events, and outcome measures including minute walking distance (MWD) test and quality of life.

Qualitative interviews are undertaken with a purposive sample of patient to capture their experiences of the study and the intervention.

Ethics and dissemination:

Ethics committee approval has been obtained. Dissemination will be through open-access publication and presentation and will seek to reach multi-professional bases as well as patient and carer groups, addressing the widespread interest in this area of research.

The study is registered in the clinical trials registry at <https://clinicaltrials.gov/show/NCT03135925>.

STRENGTHS AND LIMITATIONS

- To the best of our knowledge this will be the first research of its kind
- It will provide evidence of the acceptability of pre-habilitation to patients with myeloma and the potential for future studies
- It will not provide evidence of the effectiveness of pre-habilitation, but will inform future study design for evaluating effectiveness

INTRODUCTION

Myeloma is an incurable malignancy of antibody producing B lymphocytes and plasma cells. Equating to 7 new cases per 100,000 population in the UK, it represents 10% of all new haematological cancers.¹ Disease symptoms include anaemia and hypercalcaemia causing fatigue and weakness, immunosuppression and lytic lesions of bone increasing pathological fracture risk.²

Due to developments in disease management, life expectancy has increased significantly in the last 10 years.³ The 5 year relative survival rate for England was 42.2% in 2011,⁴ and is set to increase further due to earlier interventions in the disease process, more effective chemotherapies and increased use of autologous stem cell transplantation.⁵

Following diagnosis of multiple myeloma, the standard of care treatment for younger patients (generally, but not exclusively, under the age of 70) with adequate fitness consists of an intensive pathway commencing with induction treatment using a variety of regimens delivered as an outpatient or day case given to control disease until maximum response is achieved (usually reflected by a plateau in serum paraprotein).⁶⁻⁸ This response is then consolidated with autologous

stem cell transplantation which permits the administration of high dose myeloablative melphalan chemotherapy, a procedure typically requiring around 3 weeks inpatient care, after which patients take several months to make a functional recovery.⁶⁻⁸ The procedure is non-curative and relapse/progression of myeloma occurs after an average of 2-3 years, which requires re-institution of induction treatment, and, in many patients, consolidation with a second autologous transplant procedure.^{9,10}

Rationale for the study

Increased survival rates equates to more patients living with the burden of both the disease and its treatment for increasing numbers of years, rendering myeloma a long term condition.¹¹ The cumulative effects of the disease, compounded with the debilitating toxic nature of the treatment, impact significantly on quality of life for patients beyond the end of treatment, with late-effects symptoms including infection, fatigue, metabolic, neurological and cardiovascular disorders, as well as pain, physical fitness and psychological concerns.¹²

Only 20% of myeloma patients meet national physical activity guidelines post-treatment¹² and activity declines through treatment due to perceived barriers to exercise including pain, fear of injury and fatigue.¹³ Although research evidence in physical activity has been demonstrated to be limited,¹⁵ evidence exists to demonstrate the benefits of exercise for patients recovering from stem cell transplantation.¹⁴ Pre-rehabilitation after treatment in myeloma patients has been shown to improve symptoms of physical performance, muscle strength, aerobic capacity, psychological outcomes immunological function and fatigue.¹⁶ Exercise training for myeloma survivors has been shown to be safe and feasible during treatment with high attendance and adherence¹⁷ and has been implemented widely in clinical practice.

Studies demonstrate that pre-transplant patients have reduced exercise capacity and increased comorbidities compared with a normal population, yet most rehabilitative interventions occur during and after treatment.¹⁴ Thus while exercise rehabilitation after treatment for myeloma can be effective, we must also consider rehabilitative interventions prior to the start of treatment: pre-rehabilitation, defined as,

*“a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment ... provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments”.*¹⁸

Examples of pre-rehabilitation exist in other clinical specialties: it has been used for some time in orthopaedic surgery to improve outcomes and postoperative recovery,¹⁹ and its economic benefits have been demonstrated within colorectal surgery.²⁰ A review of pre-rehabilitation in pre-surgical cancer patients demonstrated the effective use of aerobic interventions in the management of patients undergoing thoracic surgery for lung cancer, identified the potential for its use in other oncology settings and called for further research to evaluate pre-rehabilitation for wider groups of cancer patients.¹⁹

Guidelines for the management of late and long terms effects of myeloma recommend that regular physical activity, including pre-rehabilitation and rehabilitation, and aspiration to a general healthy lifestyles, are integral to patient care pathways.¹²

Autologous stem cell transplantation in myeloma has become the commonest indication for transplantation, with, for example, over 1400 performed in the UK annually, and procedures are performed in what is normally considered an elderly patient population, many with comorbidities and frailty. It is an intensive toxic procedure, with a recovery period of at least 6 months and strategies to improve recovery are warranted, including pre-rehabilitation. A window of opportunity – usually a period of 4-6 months exists to offer pre-rehabilitation between diagnosis or relapse and the commencement of the autologous stem cell transplantation process. Coleman et al.²¹ studied 24 multiple myeloma patients undergoing a home based exercise program during chemotherapy and stem cell transplantation and identified that no patient injured themselves and that the intervention

had positive effects on lean body weight, fatigue and sleep disturbance. Despite this, no evidence currently exists regarding the use of pre-habilitation exercise interventions in multiple myeloma.

This article describes the protocol for a study underway investigating the feasibility of research into the provision of an exercise intervention in patients with myeloma who are due to receive autologous stem cell transplantation.

AIMS AND OBJECTIVES

The aim of this study is to determine whether it is feasible to conduct a randomised controlled trial into pre-transplant exercise for patients with multiple myeloma who are awaiting autologous stem cell transplantation.

We will determine this through completion of the following objectives:

1. Assess the acceptability of the study to patients by measuring recruitment and retention to the study and through qualitative interview responses
2. Explore reasons for non-consent to study participation
3. Establish whether a target cohort of patients exists.
4. Determine the most appropriate recruitment points post diagnosis through steering group feedback, recruitment rate when compared with numbers invited to join the study and qualitative interview reports
5. Assess the suitability of inclusion and exclusion criteria by examining recruitment data
6. Assess the acceptability of the intervention through qualitative interviews and retention rates during the study
7. Determine duration of the intervention before transplantation commences by monitoring point of recruitment to the study and time to transplant
8. Explore the appropriateness of outcome measures/completeness by qualitative interview responses, completion rates, time to complete.

METHODS AND ANALYSIS

Methodology

Mixed methods, combining qualitative and quantitative data collection and analysis, are used to achieve the described aims and objectives.

Design

This is a prospective feasibility study – see Figure 1 for study flow chart.

Setting

Assessments and exercise sessions take place in the physiotherapy outpatient department in an acute hospital trust, which is a regional specialist centre for haematological services. Patient interviews take place in private rooms in the physiotherapy department or over the telephone for patient convenience.

Feasibility

The feasibility of the intervention is determined through the following targets:

- Recruitment: based on patient numbers at the study site, the recruitment target is 24 patients in a 12 month period (i.e. 2 patients per month);
- Attendance: minimum average attendance at exercise sessions of 66% of the scheduled/invited sessions;
- Retention: 80% patient retention to 6-week follow up assessment;
- Adverse events: adverse events are closely monitored and use to inform decisions to proceed.

Acceptability of the intervention to patients is also determined through the qualitative data collection and analysis, described in a later section.

Quantitative Data Collection and Analysis

Data collection will take place between September 2016 and February 2018.

Sampling

Consecutive sampling is used to recruit patients to this study who have a diagnosis of multiple myeloma and have been assigned to the autologous transplantation list. The recruiting centre transplants approximately 70 myeloma patients per year: sampling all patients over a 12 month period will indicate study recruitment feasibility. This feasibility study did not have a formal sample size calculation to determine a priori the number of participants to recruit; it aimed to recruit for a fixed period of time (12 months) at a single centre and one of the outcomes was to estimate the recruitment rate per month.

Inclusion criteria

All patients with a diagnosis of multiple myeloma, assigned to the autologous transplantation waiting list for either a first or second transplant.²²

Exclusion Criteria

To allow safe completion of initial objective assessments, patients with a history of unstable angina or heart attack in the previous month are excluded.²³ Medical stability is a pre-requisite for transplantation, therefore no patients are excluded on this basis.

Recruitment

Patients are screened at clinic appointments by the bone marrow transplant team during their preparation for transplant. Patients meeting the inclusion criteria are provided with verbal and written information and invited to be involved in the study. Follow-up takes place after 48 hours via a phone call from a study physiotherapist: any remaining questions are discussed and if the patient agrees to take part then written consent is obtained and an initial assessment appointment is made.

Patients who choose not to join the study are invited to take part in a qualitative interview to explore their reasoning (Figure 1). This is described in more detail under Qualitative Data Collection and Analysis.

Intervention:

Initial Assessment

Patients attend an initial assessment with a study physiotherapist who undertakes the following:

- explanation of the pre-habilitation programme
- documentation of written consent
- subjective history including co-morbidities and patient goals
- induction to the gym area equipment
- provision of booklet and DVD with physical activity advice
- baseline objective assessment (Table 1)
- design of individualised gym program in line with patient abilities and goals
- completion of an initial gym circuit with close supervision.

Weeks 2-5

Patients attend weekly 1 hour physiotherapist-led group gym sessions and complete their individualised program. Supervision is available as required and programs are progressed in line with patient ability and performance.

Week 6

Completion of final gym circuit and repeat of objective assessments (Table 1).

Follow up

Patients are followed up on admission for transplant, and again on transplant discharge, for further repeat of objective assessments (Table 1).

	Recruitment	Initial Assessment	Weeks 2-5	Week 6	Transplant Admission	Transplant Discharge

Screening data	✓					
Demographic data		✓				
6 minute walk distance		✓		✓	✓	✓
PROMs		✓		✓	✓	✓
Activity data		✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓		

Table 1 - Study Data Collection

Outcome measures

The following data are captured for study participants.

Screening Data

Through initial screening and recruitment, data is collected on:

- number of patients meeting inclusion criteria
- patients accepting initial study information
- patients agreeing to attend for initial assessment
- reasons for non-participation.

Demographic data

The following demographic data is captured during the initial assessment:

- gender
- length of diagnosis
- baseline physical activity levels
- transplant history
- pre-transplant therapies received
- time to transplantation from decision to transplant
- other relevant information.

Functional measure

Patients undertake a 6 minute walk test (6MWD) before and after the exercise intervention. The six minute walk test is a useful field test of functional capacity, is safe to administer and although it has less correlation with peak oxygen capacity than the shuttle walk test, it is better tolerated by patients and is more reflective of activities of daily living as it is a submaximal exercise test.²³ The six minute walk test has been found to be a valid and reliable test in patients with cancer.²⁴

Patient Reported Outcome Measures (PROMs)

As this is a feasibility study, it is useful to determine the feasibility and acceptability of outcomes to be used. For this reason, two different sets of patient reported outcome measures (PROMs) are issued to alternate patients taking part in the study (Table 2). The data collected in the outcome measures and in the qualitative interviews will determine their value in any future studies.

Group	Category	Measure
Physical activity/fitness	Group 1	International Physical Activity Questionnaire ²⁵
	Group 2	Godin Leisure Time ²⁶
Mental wellbeing	Group 1 and 2	Warwick and Edinburgh Mental Well-being Scale ²⁷
Quality of Life	Group 1	FACT-MM ²⁸
	Group 2	EORTC QLQ C30 MY20 ²⁹
Self-efficacy for exercise	Group 1 and 2	Self-Efficacy for Exercise Scale ³⁰

Table 2 - Patient Reported Outcome Measures

Activity Data

The following activity data is collected for each participant:

- the number of gym attendances
- follow-up compliance
- withdrawals from the study and at which stage of the study these occur
- reasons for withdrawal or non-attendance.

Data Collection

Table 1 shows the full data collection schedule for the study.

Data Analysis

Flow of participants through the study is captured and the baseline clinical and demographic characteristics of consented participants assessed with appropriate summary statistics.

The data analysis for the feasibility objectives uses descriptive statistics and focuses on confidence interval estimation.

1. The feasibility of recruitment to main trial is assessed with the consent rate (defined as the ratio of no. of consented participants/no. of eligible participants) and its associated 95% confidence interval and the recruitment rate per month and its associated 95% confidence intervals. The target recruitment rate is a minimum of 2 participants per month.
2. Reporting of the number and characteristics of eligible patients approached for the study and reasons for refused consent
3. Reporting of study participant retention rates at six-week follow-up (e.g. participants with a valid 6-minute walk outcome – the probable primary outcome for the main trial) and its associated 95% confidence interval. The target is a minimum of 80% retention to 6-week follow up assessment.
4. Reporting of the number (and rate) of serious adverse events/incidents (and its associated 95% CI) experienced by the participants in the pre-transplantation period. A serious adverse event (SAE) is defined as any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
5. Reporting of the decision on primary endpoint for any main trial (current estimate suggests 80% power, two-sided, with n=610 to detect 5% [18m] difference in 6 min walk test with 10% dropout at 12m).

Qualitative data collection and analysis

Sampling and Data Collection

The aim of the qualitative data collection and analysis is to explore in greater detail patients' perceptions of the study including its acceptability, as well as barriers and facilitators to participation.

Patients who decline to take part in the exercise trial are asked if they would undertake a short telephone interview to ascertain their reasons for not taking part in the study. Participants who have already consented to take part in the trial and are undertaking the exercise programme are approached by a member of the clinical team and asked if they would be interested in taking part in a series of face-to-face or telephone interviews (Figure 1).

The interview topic guide is informed by evidence regarding acceptability and barriers and facilitators to participation from previous studies in pre-habilitation and studies of exercise in patients with multiple myeloma.^{17,21} It is also tailored to match developments and areas of interest that emerged from the quantitative data collection as the study progresses. The topic guide is flexible in order to enable exploration of individual experiences, for example, those who had fully completed the intervention compared to those who may have had only limited participation.

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3 Topic areas include: reasons for non-participation, participants' characteristics and descriptive
4 information regarding the nature of their disease management to date; the patient experience of
5 the intervention, with reference to aspects that may impact the design of future study e.g.
6 recruitment, ease or difficulty of attendance, timing and nature of data collection, suitability of
7 outcome measures; barriers and enablers to participation in the study.

8 Qualitative Analysis

9 The Framework Approach is used to analyse the qualitative data.³¹ This method is appropriate for
10 identifying, analysing, and reporting themes and patterns within data. It is a flexible and useful
11 research tool, which can potentially provide a rich and detailed, yet simple account of data. Early on
12 in the analysis the transcripts are repeatedly read to develop an understanding of the breadth and
13 depth of the data. During this process, data are labelled and coded in an iterative process whereby
14 patterns and sequences of content over time are identified within and across all the participants.
15 Emergent themes are further developed and refined by analysing similarities and divergences
16 between and within the participants, to form a coherent pattern³².

18 **ETHICS AND DISSEMINATION**

19 Ethical Consideration

20 Ethical approval for this study was obtained from NHS Health Research Authority - Yorkshire and
21 Humber reference 16/YH/0304.

22 Ethical issues relating to informed consent and confidentiality are addressed throughout. It is
23 acknowledged that patients approached and participating in this study may be physically debilitated
24 and experiencing anxiety, having received a new cancer diagnosis and awaiting a challenging
25 programme of treatment. Due care and diligence are taken when consenting potential subjects and
26 the option to withdraw from the study at any point is reiterated. In particular, the nature of
27 qualitative interviews, focusing on personal experiences of illness and treatment, may result in some
28 distress to some participants. The researchers have relevant experience in working with patients
29 with life-threatening illness and are skilled at talking to them, as well as being able to recognise
30 patient distress.

31 Dissemination

32 This study has involvement from, and relevance to, the professions of physiotherapy, medicine and
33 nursing. Dissemination will incorporate each of these professions and reach into the wider
34 healthcare community. We will seek to share the findings of the study through local, national and
35 international channels.

36 Patient involvement in the project has been through representation in study design and on the
37 project steering group from the North Trent Cancer Research Network Consumer Research Panel.
38 We will liaise with this group to invite ideas regarding dissemination to study participants, patients
39 and carers.

40 Where the findings of the study have implications for the provision of new or existing services to
41 patients with myeloma, we will ensure dissemination to relevant key opinion leaders and
42 stakeholders to support decision making.

43 The study is registered in the clinical trials registry at <https://clinicaltrials.gov/show/NCT03135925>.

44 **DISCUSSION**

45 It is anticipated that this study will demonstrate the feasibility of conducting research into pre-
46 habilitation physical activity programmes. Factors likely to affect feasibility may include: patient
47 perception of role of physical activity; patient time commitments; patient wellness to take part;
48 patient enjoyment of exercise.

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3 If feasibility is confirmed then we will seek to establish a larger scale study to test the efficacy of the
4 intervention. The findings from this study will be used to support power and sample size
5 calculations and to establish suitable outcome measures for future studies.

6 If the feasibility criteria are not satisfied then there will be lessons to learn regarding the potential
7 for future studies in the field, or modifications to the intervention or study design if further study is
8 indicated. Since pre-habilitation is an area of growing interest in other clinical areas, including other
9 cancer and non-cancer pathologies, then it is anticipated that the findings of this study will also be of
10 interest to practitioners considering pre-habilitation outside of myeloma.

11 Establishing the feasibility of research in this field is important to explore the case for pre-
12 habilitation. The effects of bone marrow transplantation can have a high cost to the individual and
13 to health services. There is clearly value in exploring treatment options that may lessen the effects
14 of treatment, particularly those with relatively low associated costs such as exercise pre-habilitation.

15 16 17 **CONTRIBUTORS**

18 JD conceived of the idea and secured funding with CK, JAS, KC, DG, SW and SM, who is the Chief
19 Investigator. Ethics and research governance applications were made by SM, CK and HR. JS, HR and
20 LS provided intellectual input and study design for the final protocol of the study.

21 22 **DATA SHARING STATEMENT**

23 As the paper relates to a study protocol, there are no additional data sets available as yet

24 25 **FUNDING**

26 The research was funded by the NIHR Research for Patient Benefit (RfPB) Programme PB-PG-0214-
27 33067. The views expressed are those of the author(s) and not necessarily those of the NHS, the
28 NIHR or the Department of Health.

29 30 31 **FIGURE LEGEND**

32 Figure 1 - Recruitment and Intervention Flow Chart

33 34 **REFERENCES**

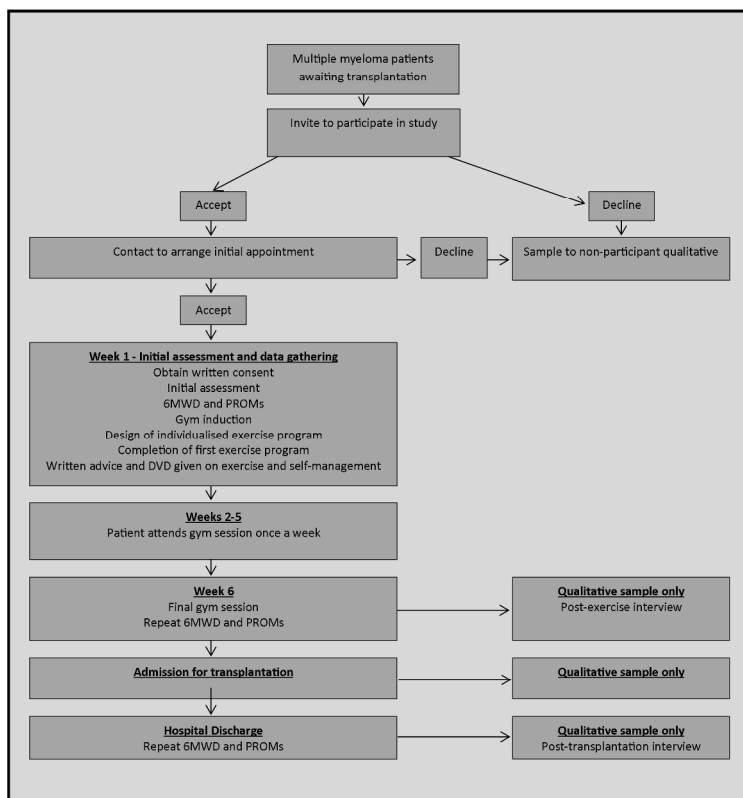
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COMPETING INTERESTS

Professor Walters reports personal fees from Book Royalties, grants from NIHR and MRC, personal fees from External examining.



Retention and Intervention Flow Chart

209x297mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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1			
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how
13		17b	If blinded, circumstances under which unblinding is permissible, and
14			procedure for revealing a participant's allocated intervention during
15			the trial
16			
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Methods: Data collection, management, and analysis

20			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol
27		18b	Plans to promote participant retention and complete follow-up,
28			including list of any outcome data to be collected for participants who
29			discontinue or deviate from intervention protocols
30			
31	Data	19	Plans for data entry, coding, security, and storage, including any
32	management		related processes to promote data quality (eg, double data entry;
33			range checks for data values). Reference to where details of data
34			management procedures can be found, if not in the protocol
35			
36	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
37	methods		Reference to where other details of the statistical analysis plan can be
38			found, if not in the protocol
39		20b	Methods for any additional analyses (eg, subgroup and adjusted
40			analyses)
41		20c	Definition of analysis population relating to protocol non-adherence
42			(eg, as randomised analysis), and any statistical methods to handle
43			missing data (eg, multiple imputation)
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Methods: Monitoring

52			
53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
54			and reporting structure; statement of whether it is independent from
55			the sponsor and competing interests; and reference to where further
56			details about its charter can be found, if not in the protocol.
57			Alternatively, an explanation of why a DMC is not needed
58			
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1			
2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
7			spontaneously reported adverse events and other unintended effects
8			of trial interventions or trial conduct
9			
10			
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
12			whether the process will be independent from investigators and the
13			sponsor
14			

Ethics and dissemination

15			
16			
17	Research ethics	24	Plans for seeking research ethics committee/institutional review board
18	approval		(REC/IRB) approval
19			
20			
21	Protocol	25	Plans for communicating important protocol modifications (eg,
22	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
23			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
24			regulators)
25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
27			participants or authorised surrogates, and how (see Item 32)
28			
29		26b	Additional consent provisions for collection and use of participant data
30			and biological specimens in ancillary studies, if applicable
31			
32			
33	Confidentiality	27	How personal information about potential and enrolled participants will
34			be collected, shared, and maintained in order to protect confidentiality
35			before, during, and after the trial
36			
37	Declaration of	28	Financial and other competing interests for principal investigators for
38	interests		the overall trial and each study site
39			
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41	Access to data	29	Statement of who will have access to the final trial dataset, and
42			disclosure of contractual agreements that limit such access for
43			investigators
44			
45	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
46	post-trial care		compensation to those who suffer harm from trial participation
47			
48	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
49	policy		participants, healthcare professionals, the public, and other relevant
50			groups (eg, via publication, reporting in results databases, or other
51			data sharing arrangements), including any publication restrictions
52			
53		31b	Authorship eligibility guidelines and any intended use of professional
54			writers
55			
56			
57		31c	Plans, if any, for granting public access to the full protocol, participant-
58			level dataset, and statistical code
59			
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

For peer review only

BMJ Open

Is it feasible to conduct a randomised controlled trial of pre-transplant exercise (pre-habilitation) for multiple myeloma patients awaiting autologous haematopoietic stem cell transplantation? Protocol for the PREeMPT study.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-021333.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Jan-2018
Complete List of Authors:	Keen, Carol; Sheffield Teaching Hospitals NHS Foundation Trust, Acute Therapy Services Skilbeck, Julie; Sheffield Hallam University, Nursing Ross, Helen; Sheffield Teaching Hospitals NHS Foundation Trust, Acute Therapy Services Smith, Lauren; Sheffield Teaching Hospitals NHS Foundation Trust, Acute Therapy Services Collins, Karen; Sheffield Hallam University, Centre for Health and Social Care Research Dixey, Joanne; Sheffield Teaching Hospitals NHS Foundation Trust Walters, Stephen; University of Sheffield, SchARR Greenfield, Diana; Sheffield Teaching Hospitals NHS Foundation Trust Snowden, John; Sheffield Teaching Hospitals NHS Foundation Trust, Department of Haematology Mawson, Susan; University of Sheffield, School of Health and Related Research
Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Myeloma < HAEMATOLOGY, Bone marrow transplantation < HAEMATOLOGY, Rehabilitation medicine < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

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5 **Title:** **Is it feasible to conduct a randomised controlled trial of**
6 **pre-transplant exercise (pre-habilitation) for multiple**
7 **myeloma patients awaiting autologous haematopoietic**
8 **stem cell transplantation? Protocol for the PREeMPT**
9 **study.**
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17 **FUNDING:** This is an original research study funded by NIHR Research for Patient Benefit
18 (RfPB) funding
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20

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ABSTRACT

Introduction:

While myeloma is an incurable malignancy, developments in disease management have led to increased life expectancy in recent years. Treatment typically involves stem-cell transplantation. Increased survival rates equates to more patients living with the burden of both the disease and its treatment for increasing numbers of years, rendering myeloma a long term condition.

Evidence exists to demonstrate the benefits of exercise for patients recovering from stem cell transplantation, and pre-habilitation – exercise before treatment - has been shown to be effective in other disease areas. To date there has been no research into pre-habilitation in myeloma patients awaiting transplantation treatment.

Our objective is to determine whether it is feasible to conduct a randomised controlled trial into pre-transplant exercise for patients with multiple myeloma who are awaiting autologous stem cell transplantation.

Methods and analysis:

This mixed methods study identifies patients with diagnosis of multiple myeloma who have been assigned to the autologous transplantation list and invites them to participate in 6 weekly sessions of individualised, supervised exercise whilst awaiting transplantation.

Quantitative data to determine feasibility targets include rates of recruitment, adherence and adverse events, and outcome measures including six minute walking distance (6MWD) test and quality of life.

Qualitative interviews are undertaken with a purposive sample of patient to capture their experiences of the study and the intervention.

Ethics and dissemination:

Ethics committee approval has been obtained. Dissemination will be through open-access publication and presentation and will seek to reach multi-professional bases as well as patient and carer groups, addressing the widespread interest in this area of research.

The study is registered in the clinical trials registry at <https://clinicaltrials.gov/show/NCT03135925>.

STRENGTHS AND LIMITATIONS

- The sample size for the qualitative aspect of this study is likely to be small – it is intended to inform future study design rather than provide
- For practical reasons, and to encourage patient recruitment, time points for data collection are aligned with clinical interventions, rather than specifically for research purposes. They are therefore subject to variation, and not within the control of the study team.
- As a feasibility study, this will not provide evidence of the effectiveness of pre-habilitation, but will inform future study design for evaluating effectiveness

INTRODUCTION

Myeloma is an incurable malignancy of antibody producing B lymphocytes and plasma cells. Equating to 7 new cases per 100,000 population in the UK, it represents 10% of all new haematological cancers.¹ Disease symptoms include anaemia and hypercalcaemia causing fatigue and weakness, immunosuppression and lytic lesions of bone increasing pathological fracture risk.²

Due to developments in disease management, life expectancy has increased significantly in the last 10 years.³ The 5 year relative survival rate for England was 42.2% in 2011,⁴ and is set to increase further due to earlier interventions in the disease process, more effective chemotherapies and increased use of autologous stem cell transplantation.⁵

Following diagnosis of multiple myeloma, the standard of care treatment for younger patients (generally, but not exclusively, under the age of 70) with adequate fitness consists of an intensive pathway commencing with induction treatment using a variety of regimens delivered as an

1
2
3 outpatient or day case given to control disease until maximum response is achieved (usually
4 reflected by a plateau in serum paraprotein).⁶⁻⁸ This response is then consolidated with autologous
5 stem cell transplantation which permits the administration of high dose myeloablative melphalan
6 chemotherapy, a procedure typically requiring around 3 weeks inpatient care, after which patients
7 take several months to make a functional recovery.⁶⁻⁸ The procedure is non-curative and
8 relapse/progression of myeloma occurs after an average of 2-3 years, which requires re-institution
9 of induction treatment, and, in many patients, consolidation with a second autologous transplant
10 procedure.^{9,10}

11 **Rationale for the study**

12 Increased survival rates equates to more patients living with the burden of both the disease and its
13 treatment for increasing numbers of years, rendering myeloma a long term condition.¹¹ The
14 cumulative effects of the disease, compounded with the debilitating toxic nature of the treatment,
15 impact significantly on quality of life for patients beyond the end of treatment, with late-effects
16 symptoms including infection, fatigue, metabolic, neurological and cardiovascular disorders, as well
17 as pain, physical fitness and psychological concerns.¹²

18
19 Only 20% of myeloma patients meet national physical activity guidelines post-treatment¹² and
20 activity declines through treatment due to perceived barriers to exercise including pain, fear of
21 injury and fatigue.¹³ Although research evidence in physical activity has been demonstrated to be
22 limited,¹⁴ evidence exists to demonstrate the benefits of exercise for patients recovering from stem
23 cell transplantation.¹⁵ Pre-habilitation after treatment in myeloma patients has been shown to
24 improve symptoms of physical performance, muscle strength, aerobic capacity, psychological
25 outcomes immunological function and fatigue.¹⁶ Exercise training for myeloma survivors has been
26 shown to be safe and feasible during treatment with high attendance and adherence¹⁷ and has been
27 implement widely in clinical practice.

28
29 Studies demonstrate that pre-transplant patients have reduced exercise capacity and increased co-
30 morbidities compared with a normal population, yet most rehabilitative interventions occur during
31 and after treatment.¹⁵ Thus while exercise rehabilitation after treatment for myeloma can be
32 effective, we must also consider rehabilitative interventions prior to the start of treatment: pre-
33 habilitation, defined as,

34
35 *“a process on the continuum of care that occurs between the time of cancer diagnosis and*
36 *the beginning of acute treatment ... provides targeted interventions that improve a patient's*
37 *health to reduce the incidence and the severity of current and future impairments”.*¹⁸

38
39 Examples of pre-habilitation exist in other clinical specialties: it has been used for some time in
40 orthopaedic surgery to improve outcomes and postoperative recovery,¹⁹ and its economic benefits
41 have been demonstrated within colorectal surgery.²⁰ A review of pre-habilitation in pre-surgical
42 cancer patients demonstrated the effective use of aerobic interventions in the management of
43 patients undergoing thoracic surgery for lung cancer, identified the potential for its use in other
44 oncology settings and called for further research to evaluate pre-habilitation for wider groups of
45 cancer patients.¹⁹

46
47 Guidelines for the management of late and long terms effects of myeloma recommend that regular
48 physical activity, including pre-habilitation and rehabilitation, and aspiration to a general healthy
49 lifestyles, are integral to patient care pathways.¹²

50
51 Autologous stem cell transplantation in myeloma has become the commonest indication for
52 transplantation, with, for example, over 1400 performed in the UK annually, and procedures are
53 performed in what is normally considered an elderly patient population, many with comorbidities
54 and frailty. It is an intensive toxic procedure, with a recovery period of at least 6 months and
55 strategies to improve recovery are warranted, including pre-habilitation. A window of opportunity –
56 usually a period of 4-6 months exists to offer pre-habilitation between diagnosis or relapse and the
57 commencement of the autologous stem cell transplantation process. Coleman et al.²¹ studied 24

multiple myeloma patients undergoing a home based exercise program during chemotherapy and stem cell transplantation and identified that no patient injured themselves and that the intervention had positive effects on lean body weight, fatigue and sleep disturbance. Despite this, no evidence currently exists regarding the use of pre-habilitation exercise interventions in multiple myeloma.

This article describes the protocol for a study underway investigating the feasibility of research into the provision of an exercise intervention in patients with myeloma who are due to receive autologous stem cell transplantation.

AIMS AND OBJECTIVES

The aim of this study is to determine whether it is feasible to conduct a randomised controlled trial into pre-transplant exercise for patients with multiple myeloma who are awaiting autologous stem cell transplantation.

We will determine this through completion of the following objectives:

1. Assess the acceptability of the study to patients by measuring recruitment and retention to the study and through qualitative interview responses
2. Explore reasons for non-consent to study participation
3. Establish whether a target cohort of patients exists.
4. Determine the most appropriate recruitment points post diagnosis through steering group feedback, recruitment rate when compared with numbers invited to join the study and qualitative interview reports
5. Assess the suitability of inclusion and exclusion criteria by examining recruitment data
6. Assess the acceptability of the intervention through qualitative interviews and retention rates during the study
7. Determine duration of the intervention before transplantation commences by monitoring point of recruitment to the study and time to transplant
8. Explore the appropriateness of outcome measures/completeness by qualitative interview responses, completion rates, time to complete.

METHODS AND ANALYSIS

Methodology

Mixed methods, combining qualitative and quantitative data collection and analysis, are used to achieve the described aims and objectives.

Design

This is a prospective feasibility study – see Figure 1 for study flow chart.

Setting

Assessments and exercise sessions take place in the physiotherapy outpatient department in an acute hospital trust, which is a regional specialist centre for haematological services. Patient interviews take place in private rooms in the physiotherapy department or over the telephone for patient convenience.

Feasibility

The feasibility of the intervention is determined through the following targets:

- Recruitment: based on patient numbers at the study site, the recruitment target is 24 patients in a 12 month period (i.e. 2 patients per month);
- Attendance: minimum average attendance at exercise sessions of 66% of the scheduled/invited sessions;
- Retention: 80% patient retention to 6-week follow up assessment;
- Adverse events: adverse events are closely monitored and use to inform decisions to proceed.

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3 Acceptability of the intervention to patients is also determined through the qualitative data
4 collection and analysis, described in a later section.

5 **Quantitative Data Collection and Analysis**

6 Data collection will take place between September 2016 and February 2018.

7 Sampling

8 Consecutive sampling is used to recruit patients to this study who have a diagnosis of multiple
9 myeloma and have been assigned to the autologous transplantation list. The recruiting centre
10 transplants approximately 70 myeloma patients per year: sampling all patients over a 12 month
11 period will indicate study recruitment feasibility. This feasibility study did not have a formal sample
12 size calculation to determine a priori the number of participants to recruit; it aimed to recruit for a
13 fixed period of time (12 months) at a single centre and one of the outcomes was to estimate the
14 recruitment rate per month.
15

16 Inclusion criteria

17 All patients with a diagnosis of multiple myeloma, assigned to the autologous transplantation
18 waiting list for either a first or second transplant.²²

19 Exclusion Criteria

20 To allow safe completion of initial objective assessments, patients with a history of unstable angina
21 or heart attack in the previous month are excluded.²³ Medical stability is a pre-requisite for
22 transplantation, therefore no patients are excluded on this basis.
23

24 Recruitment

25 Patients are screened at clinic appointments by the bone marrow transplant team during their
26 preparation for transplant. Patients meeting the inclusion criteria are provided with verbal and
27 written information and invited to be involved in the study. Follow-up takes place after 48 hours via
28 a phone call from a study physiotherapist: any remaining questions are discussed and if the patient
29 agrees to take part then written consent is obtained and an initial assessment appointment is made.
30

31 Patients who choose not to join the study are invited to take part in a qualitative interview to
32 explore their reasoning (Figure 1). This is described in more detail under Qualitative Data Collection
33 and Analysis.

34 Intervention:

35 *Initial Assessment*

36 Patients attend an initial assessment with a study physiotherapist who undertakes the following:

- 37 • explanation of the pre-habilitation programme
- 38 • documentation of written consent
- 39 • subjective history including co-morbidities and patient goals
- 40 • induction to the gym area equipment
- 41 • provision of booklet and DVD with physical activity advice
- 42 • baseline objective assessment (Table 1)
- 43 • design of individualised gym program in line with patient abilities and goals
- 44 • completion of an initial gym circuit with close supervision.

45 *Weeks 2-5*

46 Patients attend weekly 1 hour physiotherapist-led group gym sessions and complete their
47 individualised program. Supervision is available as required and programs are progressed in line
48 with patient ability and performance.
49

50 *Week 6*

51 Completion of final gym circuit and repeat of objective assessments (Table 1).
52

53 *Follow up*

54 Patients are followed up on admission for transplant, and again on transplant discharge, for further
55 repeat of objective assessments (Table 1).
56
57

	Recruitment	Initial Assessment	Weeks 2-5	Week 6	Transplant Admission	Transplant Discharge
Screening data	✓					
Demographic data		✓				
6 minute walk distance		✓		✓	✓	✓
PROMs		✓		✓	✓	✓
Activity data		✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓		

Table 1 - Study Data Collection

Outcome measures

The following data are captured for study participants.

Screening Data

Through initial screening and recruitment, data is collected on:

- number of patients meeting inclusion criteria
- patients accepting initial study information
- patients agreeing to attend for initial assessment
- reasons for non-participation.

Demographic data

The following demographic data is captured during the initial assessment:

- gender
- length of diagnosis
- baseline physical activity levels
- transplant history
- pre-transplant therapies received
- time to transplantation from decision to transplant
- other relevant information.

Functional measure

Patients undertake a 6 minute walk test (6MWD) before and after the exercise intervention. The six minute walk test is a useful field test of functional capacity, is safe to administer and although it has less correlation with peak oxygen capacity than the shuttle walk test, it is better tolerated by patients and is more reflective of activities of daily living as it is a submaximal exercise test.²³ The six minute walk test has been found to be a valid and reliable test in patients with cancer.²⁴

Patient Reported Outcome Measures (PROMs)

As this is a feasibility study, it is useful to determine the feasibility and acceptability of outcomes to be used. For this reason, two different sets of patient reported outcome measures (PROMs) are issued to alternate patients taking part in the study (Table 2). The data collected in the outcome measures and in the qualitative interviews will determine their value in any future studies.

Group	Category	Measure
Physical activity/fitness	Group 1	International Physical Activity Questionnaire ²⁵
	Group 2	Godin Leisure Time ²⁶
Mental wellbeing	Group 1 and 2	Warwick and Edinburgh Mental Well-being Scale ²⁷
Quality of Life	Group 1	FACT-MM ²⁸

	Group 2	EORTC QLQ C30 MY20 ²⁹
Self-efficacy for exercise	Group 1 and 2	Self-Efficacy for Exercise Scale ³⁰

Table 2 - Patient Reported Outcome Measures

Activity Data

The following activity data is collected for each participant:

- the number of gym attendances
- follow-up compliance
- withdrawals from the study and at which stage of the study these occur
- reasons for withdrawal or non-attendance.

Data Collection

Table 1 shows the full data collection schedule for the study.

Data Analysis

Flow of participants through the study is captured and the baseline clinical and demographic characteristics of consented participants assessed with appropriate summary statistics.

The data analysis for the feasibility objectives uses descriptive statistics and focuses on confidence interval estimation.

1. The feasibility of recruitment to main trial is assessed with the consent rate (defined as the ratio of no. of consented participants/no. of eligible participants) and its associated 95% confidence interval and the recruitment rate per month and its associated 95% confidence intervals. The target recruitment rate is a minimum of 2 participants per month.
2. Reporting of the number and characteristics of eligible patients approached for the study and reasons for refused consent
3. Reporting of study participant retention rates at six-week follow-up (e.g. participants with a valid 6-minute walk outcome – the probable primary outcome for the main trial) and its associated 95% confidence interval. The target is a minimum of 80% retention to 6-week follow up assessment.
4. Reporting of the number (and rate) of serious adverse events/incidents (and its associated 95% CI) experienced by the participants in the pre-transplantation period. A serious adverse event (SAE) is defined as any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
5. Reporting of the decision on primary endpoint for any main trial (current estimate suggests 80% power, two-sided, with n=610 to detect 5% [18m] difference in 6 min walk test with 10% dropout at 12m).

Qualitative data collection and analysis

Sampling and Data Collection

The aim of the qualitative data collection and analysis is to explore in greater detail patients' perceptions of the study including its acceptability, as well as barriers and facilitators to participation.

Patients who decline to take part in the exercise trial are asked if they would undertake a short telephone interview to ascertain their reasons for not taking part in the study. Participants who have already consented to take part in the trial and are undertaking the exercise programme are approached by a member of the clinical team and asked if they would be interested in taking part in a series of face-to-face or telephone interviews (Figure 1).

The interview topic guide is informed by evidence regarding acceptability and barriers and facilitators to participation from previous studies in pre-rehabilitation and studies of exercise in patients with multiple myeloma.^{17,21} It is also tailored to match developments and areas of interest

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3 that emerged from the quantitative data collection as the study progresses. The topic guide is
4 flexible in order to enable exploration of individual experiences, for example, those who had fully
5 completed the intervention compared to those who may have had only limited participation.

6 Topic areas include: reasons for non-participation, participants' characteristics and descriptive
7 information regarding the nature of their disease management to date; the patient experience of
8 the intervention, with reference to aspects that may impact the design of future study e.g.
9 recruitment, ease or difficulty of attendance, timing and nature of data collection, suitability of
10 outcome measures; barriers and enablers to participation in the study.

11 Qualitative Analysis

12 The Framework Approach is used to analyse the qualitative data.³¹ This method is appropriate for
13 identifying, analysing, and reporting themes and patterns within data. It is a flexible and useful
14 research tool, which can potentially provide a rich and detailed, yet simple account of data. Early on
15 in the analysis the transcripts are repeatedly read to develop an understanding of the breadth and
16 depth of the data. During this process, data are labelled and coded in an iterative process whereby
17 patterns and sequences of content over time are identified within and across all the participants.
18 Emergent themes are further developed and refined by analysing similarities and divergences
19 between and within the participants, to form a coherent pattern³².

22 **ETHICS AND DISSEMINATION**

23 Ethical Consideration

24 Ethical approval for this study was obtained from NHS Health Research Authority - Yorkshire and
25 Humber reference 16/YH/0304.

26 Ethical issues relating to informed consent and confidentiality are addressed throughout. It is
27 acknowledged that patients approached and participating in this study may be physically debilitated
28 and experiencing anxiety, having received a new cancer diagnosis and awaiting a challenging
29 programme of treatment. Due care and diligence are taken when consenting potential subjects and
30 the option to withdraw from the study at any point is reiterated. In particular, the nature of
31 qualitative interviews, focusing on personal experiences of illness and treatment, may result in some
32 distress to some participants. The researchers have relevant experience in working with patients
33 with life-threatening illness and are skilled at talking to them, as well as being able to recognise
34 patient distress.

36 Dissemination

37 This study has involvement from, and relevance to, the professions of physiotherapy, medicine and
38 nursing. Dissemination will incorporate each of these professions and reach into the wider
39 healthcare community. We will seek to share the findings of the study through local, national and
40 international channels.

41 Patient involvement in the project has been through representation in study design and on the
42 project steering group from the North Trent Cancer Research Network Consumer Research Panel.
43 We will liaise with this group to invite ideas regarding dissemination to study participants, patients
44 and carers.

45 Where the findings of the study have implications for the provision of new or existing services to
46 patients with myeloma, we will ensure dissemination to relevant key opinion leaders and
47 stakeholders to support decision making.

48 The study is registered in the clinical trials registry at <https://clinicaltrials.gov/show/NCT03135925>.

52 **DISCUSSION**

53 It is anticipated that this study will demonstrate the feasibility of conducting research into pre-
54 habilitation physical activity programmes. Factors likely to affect feasibility may include: patient
55
56
57

perception of role of physical activity; patient time commitments; patient wellness to take part; patient enjoyment of exercise.

If feasibility is confirmed then we will seek to establish a larger scale study to test the efficacy of the intervention. The findings from this study will be used to support power and sample size calculations and to establish suitable outcome measures for future studies.

If the feasibility criteria are not satisfied then there will be lessons to learn regarding the potential for future studies in the field, or modifications to the intervention or study design if further study is indicated. Since pre-habilitation is an area of growing interest in other clinical areas, including other cancer and non-cancer pathologies, then it is anticipated that the findings of this study will also be of interest to practitioners considering pre-habilitation outside of myeloma.

Establishing the feasibility of research in this field is important to explore the case for pre-habilitation. The effects of bone marrow transplantation can have a high cost to the individual and to health services. There is clearly value in exploring treatment options that may lessen the effects of treatment, particularly those with relatively low associated costs such as exercise pre-habilitation.

CONTRIBUTORS

JD conceived of the idea and secured funding with CK, JSn, KC, DG, SW and SM, who is the Chief Investigator. Ethics and research governance applications were made by SM, CK and HR. JSk, HR and LS provided intellectual input and study design for the final protocol of the study. All authors were involved in drafting or critically revising this work, and in final approval of the version to be published.

DATA SHARING STATEMENT

As the paper relates to a study protocol, there are no additional data sets available as yet.

FUNDING

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FIGURE LEGEND

Figure 1 - Recruitment and Intervention Flow Chart

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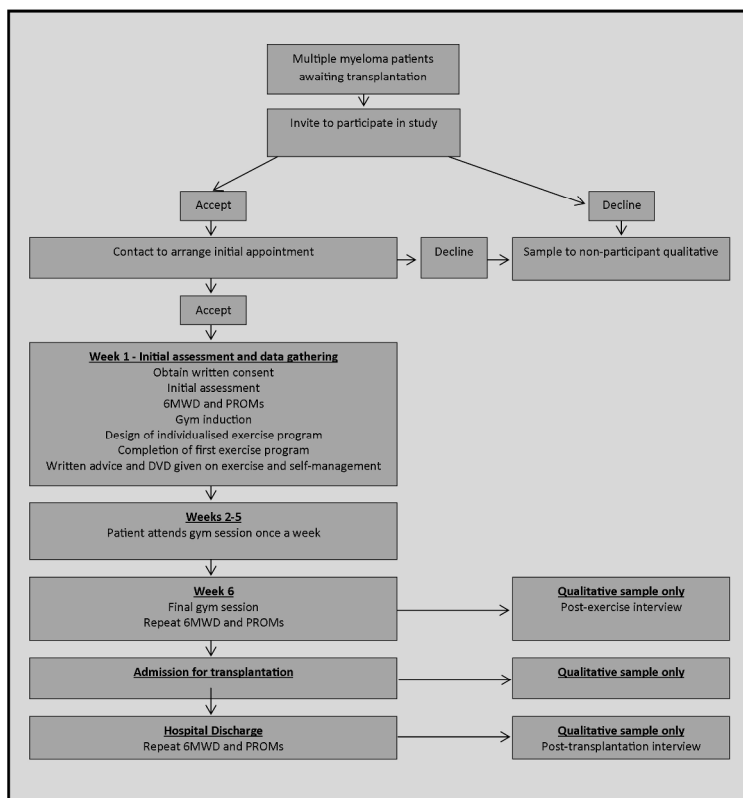
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COMPETING INTERESTS

Professor Walters reports personal fees from Book Royalties, grants from NIHR and MRC, personal fees from external examining.



Retention and Intervention Flow Chart

209x297mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	9
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	n/a
Objectives	7	Specific objectives or hypotheses	4

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Methods: Participants, interventions, and outcomes

9	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
13	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
17	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
21		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
25		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
32	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
40	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
44	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
48	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	n/a
3	generation		generated random numbers), and list of any factors for	
4			stratification. To reduce predictability of a random sequence,	
5			details of any planned restriction (eg, blocking) should be	
6			provided in a separate document that is unavailable to those	
7			who enrol participants or assign interventions	
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9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	n/a
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
11	mechanism		describing any steps to conceal the sequence until interventions	
12			are assigned	
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14	Implementation	16c	Who will generate the allocation sequence, who will enrol	n/a
15			participants, and who will assign participants to interventions	
16				
17	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial	n/a
18	(masking)		participants, care providers, outcome assessors, data analysts),	
19			and how	
20				
21		17b	If blinded, circumstances under which unblinding is permissible,	n/a
22			and procedure for revealing a participant's allocated intervention	
23			during the trial	
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25				

Methods: Data collection, management, and analysis

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27				
28	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	7
29	methods		other trial data, including any related processes to promote data	
30			quality (eg, duplicate measurements, training of assessors) and	
31			a description of study instruments (eg, questionnaires,	
32			laboratory tests) along with their reliability and validity, if known.	
33			Reference to where data collection forms can be found, if not in	
34			the protocol	
35				
36		18b	Plans to promote participant retention and complete follow-up,	n/a
37			including list of any outcome data to be collected for participants	
38			who discontinue or deviate from intervention protocols	
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40				
41	Data	19	Plans for data entry, coding, security, and storage, including any	n/a
42	management		related processes to promote data quality (eg, double data entry;	
43			range checks for data values). Reference to where details of	
44			data management procedures can be found, if not in the	
45			protocol	
46				
47	Statistical	20a	Statistical methods for analysing primary and secondary	7
48	methods		outcomes. Reference to where other details of the statistical	
49			analysis plan can be found, if not in the protocol	
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51		20b	Methods for any additional analyses (eg, subgroup and adjusted	n/a
52			analyses)	
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1		20c	Definition of analysis population relating to protocol non-	n/a
2			adherence (eg, as randomised analysis), and any statistical	
3			methods to handle missing data (eg, multiple imputation)	
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Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9

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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	n/a
3	post-trial care		compensation to those who suffer harm from trial participation	
4				
5	Dissemination	31a	Plans for investigators and sponsor to communicate trial results	8
6	policy		to participants, healthcare professionals, the public, and other	
7			relevant groups (eg, via publication, reporting in results	
8			databases, or other data sharing arrangements), including any	
9			publication restrictions	
10				
11		31b	Authorship eligibility guidelines and any intended use of	n/a
12			professional writers	
13				
14		31c	Plans, if any, for granting public access to the full protocol,	n/a
15			participant-level dataset, and statistical code	
16				
17	Appendices			
18				
19	Informed consent	32	Model consent form and other related documentation given to	n/a
20	materials		participants and authorised surrogates	
21				
22	Biological	33	Plans for collection, laboratory evaluation, and storage of	n/a
23	specimens		biological specimens for genetic or molecular analysis in the	
24			current trial and for future use in ancillary studies, if applicable	
25				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.



CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	3
	2b	Specific objectives or research questions for pilot trial	4
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
	4c	How participants were identified and consented	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	6
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	4,7
Sample size	7a	Rationale for numbers in the pilot trial	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	n/a
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	n/a
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	n/a

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	n/a
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the pilot trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	n/a
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	n/a
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
	19a	If relevant, other important unintended consequences	n/a
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	n/a
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	n/a
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	n/a
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	n/a
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	2
Protocol	24	Where the pilot trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	9
	26	Ethical approval or approval by research review committee, confirmed with reference number	8

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2 Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
3 *We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important
4 clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological
5 treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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