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Adrenalectomy for isolated metastasis from operable non-small-cell lung cancer

Priya Sastry, Adam Tocock and Aman S. Coonar*

Department of Cardiothoracic Surgery, Papworth Hospital, Papworth Everard, Cambridge, UK

* Corresponding author. Department of Cardiothoracic Surgery, Papworth Hospital, Cambridge CB23 3RE, UK. Tel/fax: +44-1480-830541; e-mail: aman.coonar@papworth.nhs.uk (A. Coonar).

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Abstract

A best evidence topic in cardiothoracic surgery was written according to a structured protocol. The question addressed was 'in [patients with isolated adrenal metastasis from operable/operated non-small cell lung cancer] is [adrenalectomy] superior [to chemo/radiotherapy alone for achieving long-term survival]?' Altogether >160 papers were found using the reported search, of which 3 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. We conclude that the body of evidence is small, retrospective and not formally controlled. As such interpretation is limited by selection bias in assignment of patients. These limitations notwithstanding, surgical resection is associated with prolonged survival for patients with isolated adrenal metastasis from non-small cell lung cancer (NSCLC). Patient selection is probably critical. Factors that are important are: otherwise early tumour, node (TN) status of the lung primary and R0 resection, long disease-free interval and confidence that there are no other sites of metastasis. Patients with ipsilateral adrenal metastasis may derive the greatest survival benefit from adrenalectomy, since spread to the ipsilateral gland may occur via direct lymphatic channels in the retroperitoneum. Involvement of the contralateral adrenal may signify haematogenous spread and therefore, a more aggressive process. Adrenalectomy must be accompanied by regional lymph node clearance to reduce the chance of further spread from the adrenal itself.

Keywords: Review • Adrenalectomy • Neoplasm metastasis • Adrenal gland neoplasms • Adrenal gland • Carcinoma non-small-cell lung

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [patients with isolated adrenal metastasis from operable/operated non-small cell lung cancer] is [adrenalectomy] superior [to chemo/radiotherapy alone for achieving long-term survival]?

CLINICAL SCENARIO

A patient is presented at a lung cancer multidisciplinary team meeting who underwent lung resection for T2N0 non-small-cell lung cancer 3 months previously. He now has an isolated metastasis in the adrenal gland. Colleagues debate whether adrenalectomy confers any survival benefit over chemo/radiotherapy.

SEARCH STRATEGY

The following search strategy was used using national health service (NHS) Evidence's Healthcare Databases Advanced Search interface.

Medline (1950–2012): terms in capitals followed by '/' represent MeSH terms. The abbreviation 'ti. ab.' specifies that preceding terms were sought in the titles or abstracts of records. The letters 'exp' indicate that the subsequent search term was exploded to included subsidiary terms.

[(isolated OR solitary) AND adrenal AND (metast* OR 'meta sta*') ti,ab.]

OR

[[((exp NEOPLASM METASTASIS/ OR metasta* ti,ab. OR 'meta sta*' ti,ab.) AND (exp ADRENAL GLANDS/ OR 'adrenal gland*' ti,ab.)) OR exp ADRENAL GLAND NEOPLASMS/ OR exp ADRENALECTOMY/ OR adrenalectom* ti,ab.]

AND

[exp CARCINOMA, NON-SMALL-CELL LUNG/ OR NSCLC ti. OR ('non small cell*' AND (lung* ADJ cancer*) ti,ab.) OR (squamous AND lung* AND (cancer* OR carcinom* OR neoplasm*) ti,ab.) OR (adenocarcinom* adj3 lung* ti,ab.)]]

A search of the Cochrane Library using the above strategy was also performed.

Embase 1980–2012 using NHS Evidence's Healthcare Databases Advanced Search interface. Terms in capitals followed by '/' represent EMTREE terms.

[(isolated OR solitary) AND adrenal AND (metast* OR 'meta sta*') ti,ab.]

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Raz *et al.* (2011) Ann Thorac Surg, USA [2] Retrospective cohort study (level 4, good)	37 patients identified with isolated adrenal metastases from NSCLC 20 underwent surgical resection 17 underwent non-operative management Maximum follow-up period 16 years	5-year survival	34% in the adrenalectomy group vs 0% in the non-operative group ($P = 0.002$) 83% for ipsilateral tumours vs 0% for contralateral tumours ($P = 0.003$) 67% in cases of lower lobe NSCLC vs 27% in cases of upper lobe tumours ($P = 0.29$) 27% synchronous metastasis vs 41% metachronous metastases ($P = 0.81$) 52% with N0 or N1 disease vs 0% with N2 disease ($P = 0.008$)	The selection process for operative vs non-operative management was inconsistent Adrenelectomy patients were on average 10 years younger 50% of patients in the adrenalectomy group (and 70% in the non-operated group) had N2 or T4 disease—therefore, the adrenal metastasis was not truly isolated Significant variability in treatment with chemotherapy and radiotherapy
Luketich and Burt (1996) USA [3] Retrospective cohort study (level 4, good)	14 patients with isolated synchronous adrenal metastasis from NSCLC 8 patients had neoadjuvant chemotherapy followed by concomitant lung resection and adrenalectomy 6 patients had only 3 cycles of chemotherapy (mitomycin, cisplatinum and vinblastine) 5-year follow-up	Median survival	Median survival 8.5 months in the chemotherapy alone group vs 31 months in the chemotherapy + surgery group In the surgically resected group, the 3-year actuarial survival was 38% Longest survivor at end follow-up was 61 months	Small study, but no significant differences seen in preoperative characteristics tumour size or cell type to otherwise explain the improved survival Authors recommend that surgery should be advocated after ensuring that curative resection of the lung primary can be achieved, the adrenal lesion is the only metastasis and that the patient has a good performance status
Higashiyama *et al.* (1994) Japan [4] Retrospective cohort study (level 4, good)	9 patients with isolated adrenal metastases from surgically resected lung cancer (4 non-curative and 5 curative) 5 treated with adrenalectomy followed by adjuvant chemo or radiotherapy 4 treated with palliative chemo ± radiotherapy Maximum follow-up 40 months	Survival	Adrenalectomy group: 2/5 alive at 24 and 40 months, respectively 3/5 died at 9, 17 and 20 months, respectively Palliative group: All died within 6 months	All patients in the palliative group had a disease-free interval of <7 months. This selection bias may explain some of the observed difference in survival in addition to the influence of treatment strategy Authors concluded that short DFIs are probably due to lymphatic spread and probable signify a more aggressive tumour. Therefore, they recommend that DFI should be one of the criteria for selecting patients for adrenalectomy

OR

[[((exp METASTASIS/ OR metasta* ti,ab. OR 'meta sta*' ti,ab.) AND (exp ADRENAL GLAND/ OR 'adrenal gland*' ti,ab.)) OR exp ADRENAL METASTASIS/ OR exp ADRENALECTOMY/ OR adrenalectom* ti,ab.]

AND [exp LUNG NON SMALL CELL CANCER/ OR NSCLC ti,ab. OR ('non small cell*' AND (lung* ADJ cancer*) ti,ab.) OR (squamous AND lung* AND (cancer* OR carcinom* OR neoplasm*) ti,ab.) OR (adenocarcinom* adj3 lung* ti,ab.)]]

An online search using the free-text terms above was also conducted using Google.

Seventy-eight papers were identified from EMBASE, 87 from MEDLINE (5 duplicated in both), none from the Cochrane Library and none from Google.

SEARCH OUTCOME

One hundred and sixty papers were found using the reported search. From these, three papers were identified that provided the best evidence to answer the question. These are presented in Table 1.

RESULTS

Only three studies compared adrenalectomy against non-surgical treatments.

Higashiyama *et al*. [4] reported on 9 patients with isolated adrenal metastasis from surgically resected NSCLC. Five patients who underwent adrenalectomy and adjuvant chemo/radiotherapy were compared against 4 patients that had palliative treatment. Mean survival was improved in the adrenalectomy group (22 months vs 3.5 months). The authors identified that the patients selected for adrenalectomy and adjuvant chemo/radiotherapy had a longer disease-free interval (DFI, mean 7.5 months in the adrenalectomy group vs 3.5 months). The authors noted that patients who otherwise had Stage I NSCLC at initial staging appeared to derive the greatest survival benefit from surgical resection of adrenal metastasis. The authors recommend that adrenalectomy should, therefore, be reserved for patients with otherwise early stage NSCLC which has been controlled, in whom the adrenal gland is the only site of metastasis and in whom the DFI is long (although this is not quantified). They also recommend resection of the lymph nodes regional to the adrenal to reduce the potential for further spread of malignancy from the metastasis itself.

The largest relevant series [2] reports a 5-year survival of 34% in the surgical group vs 0% in the non-surgical group. The surgical group did not have adjuvant chemo/radiotherapy. Selection for surgery was influenced by DFI, extent of comorbidities and patient choice. On multivariate analysis, ipsilateral adrenal gland metastasis was predictive of 5-year survival (83% in the ipsilateral group vs 0% in the contralateral group). This could be explained if ipsilateral adrenal metastasis represents a form of 'locoregional' spread via direct retroperioneal lymphatic channels between lung and adrenal gland rather than haematogenous spread. Mediastinal lymph node involvement was also predictive of worse 5-year survival.

In the series from Luketich and Burt [3], all 14 patients had synchronous adrenal metastases and were, therefore, given platinum-based chemotherapy. Eighty patients were selected for subsequent surgery, while 6 patients had chemotherapy only. The basis for this selection is stated as surgeon and patient preference. The median survival was 8.5 months in the chemotherapy alone group vs 31 months in the chemotherapy + surgery group. In the surgically resected group the 3-year actuarial survival was 38%, and the longest recorded survivor at that stage of follow-up was 61 months. The patients in the two groups were well-matched for age, sex, performance status, size of adrenal metastasis and locoregional stage of NSCLC.

Other case series in the literature have investigated other predictors of survival after adrenalectomy for isolated NSCLC metastasis. Whether the metastasis is synchronous (diagnosed within 3–6 months (definition varies in different studies) of the lung primary) or metachronous (diagnosed 3 months or longer after the lung primary) is thought to be important. Tanvetyanon *et al*. [5] performed a systematic review of 10 publications and pooled analysis of 114 patients (42% synchronous and 58% metachronous) to address this question. They identified that median survival was shorter for the patients with synchronous adrenal metastasis (12 months vs 31 months, $P = 0.2$). The median DFI was 0 in the synchronous group vs 12 months in the metachronous group.

CLINICAL BOTTOM LINE

Surgical resection is associated with increased duration of survival for selected patients with isolated adrenal metastasis from NSCLC. Factors that are probably important are:

(i) Otherwise early stage NSCLC at initial staging.
(ii) R0 resection.
(iii) Long DFI.
(iv) No evidence of other metastasis.

Ipsilateral adrenal metastasis may represent relatively early lymphatic spread, and therefore, these patients may derive more benefit from adrenalectomy. Intuitively, a favourable response to chemotherapy may identify potential treatment candidates.

Conflict of interest: none declared.

REFERENCES

[1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. Interact CardioVasc Thorac Surg 2003;2:405–9.
[2] Raz DJ, Lanuti M, Gaissert HC, Wright CD, Mathisen DJ, Wain JC. Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma. Ann Thorac Surg 2011;92:1788–92.
[3] Luketich JD, Burt ME. Does resection of adrenal metastases from non-small cell lung cancer improve survival? Ann Thorac Surg 1996;62:1614–6.
[4] Higashiyama M, Doi O, Kodama K, Yokouchi H, Imaoka S, Koyama H. Surgical treatment of adrenal metastasis following pulmonary resection for lung cancer: comparison of adrenalectomy with palliative therapy. Int Surg 1994;79:124–9.
[5] Tanvetyanon T, Robinson LA, Schell MJ, Strong VE, Kapoor R, Coit DG *et al*. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. J Clin Oncol 2008;26:1142–7.

BEST EVIDENCE TOPIC

eComment. Does adrenalectomy in lung cancer improve survival?

Authors: ***Sezai Cubuk and Orhan Yucel***
GATA Medical Faculty, Department of Thoracic Surgery, Ankara, Turkey
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We have read with great interest the review from Sastry *et al.* [1]. Surgery is the main treatment protocol for non-metastatic lung cancer. Distant metastasis is suggested as stage 4 disease and surgery is not performed for these tumours. Surgery for solitary brain metastasis has been shown to prolong survival [2]. However, adrenalectomy in non-small-cell lung cancer is controversial. Several studies have been performed [3, 4] investigating the effect of adrenalectomy in non-small cell lung cancer. As a general rule of lung cancer treatment, we do not perform surgery for lung cancer patients who have distant metastasis. But we think that patients having only adrenal metastasis with a T1-2 tumour can be considered separately from this distant metastasis group and should be discussed within a multidisciplinary approach for adrenalectomy to improve survival. We report here our institutional results of adrenalectomy in non-small-cell lung cancer patients.

We operated on three synchronous isolated adrenal metastatic lung cancer patients [5]. All patients underwent lobectomy with lymph node dissection which revealed no mediastinal involvement. The first patient was operated on after neoadjuvant