Is sublobar resection equivalent to lobectomy for surgical management of peripheral carcinoid?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was: Is sub-lobar resection equivalent to lobectomy in terms of operative morbidity and mortality, long-term survival and disease recurrence in patients with peripheral carcinoid lung cancer? A total of 342 papers were identified using the search as described below. Of these, 10 papers presented the best evidence to answer the clinical question as they presented sufficient data to reach conclusions regarding the issues of interest for this review. Long-term survival, disease recurrence and operative morbidity were included in the assessment. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of the papers are tabulated. A literature search showed that there is a good prognosis after resection of lung carcinoid with the 10-year disease-free survival rate ranging between 77 and 94%, and suggested that sub-lobar resection of a typical carcinoid did not compromise the longterm survival. The proportion of peripheral tumours ranged between 22.6 and 100% and the proportion of patients with a preoperative diagnosis of carcinoid ranged between 51.9 and 86.7%, with many series not providing either or both of these data. As a result, a lobectomy or greater resection was necessary on anatomical or diagnostic grounds and led to a low number of sub-lobar resections. Owing to the high heterogeneity within and between series and small numbers of cases included, it is difficult to draw conclusions on disease recurrence and postoperative morbidity. All studies available retrospectively compared heterogeneous groups of non-matched group of patients, which can bias the outcomes reported. There is a lack of comprehensive randomized studies to compare a lobectomy or greater resection and sub-lobar resection. We conclude that there is little objective evidence to show the equivalence or superiority of lobectomy over sub-lobar resection.

Keywords: Carcinoid · Lobectomy · Sublobar

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 peripheral carcinoid lung cancer] is [sub-lobar resection equivalent to lobectomy] in terms of [operative morbidity and mortality, long-term survival and disease recurrence]?

CLINICAL SCENARIO

A 53-year old male patient with an early stage peripheral carcinoid tumour and no mediastinal node involvement on the positron emission tomography scan is referred for lung resection. He is a non-smoker with normal lung function. His case is discussed at the Multidiscplinary team meeting and the question is whether a sublobar resection, as a less invasive surgery than lobectomy, would carry similar survival and cancer recurrence rates.

SEARCH STRATEGY

Medline from 1950 to September 2012 using the PubMed interface ('Carcinoid tumour' [Mesh]) AND (Pulmonary Surgical Procedures [Mesh]). The search was limited to English language articles and human studies only. This search was repeated in the Cochrane Central Register of Controlled Trials. In addition, the reference lists of each publication were searched.

SEARCH OUTCOME

A total of 342 papers were found using the reported search. From these, 10 papers provided the best evidence to answer the question. These are presented in Table 1.

RESULTS

There is good prognosis after resection of the lung carcinoid with the 10-year disease-free survival rate ranging between 77 and 94% [2, 3]. Multiple studies have identified atypical histology

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Table 1: Summary table						
Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments		
McCaughan <i>et al.</i> (1985), J Thorac Cardiovasc Surg, USA [2] Retrospective cohort study (level 2b)	Single-centre retrospective study: Between 1949 and 1983, 124 patients, 101 had resection (80 had a lobectomy or greater resection), 15 had a segmentectomy or wedge resection, 6 had endobronchial resection. 72 of the 95 tumours resected, 72 (75.8%) were typical carcinoid Median age: 55 years (12–82 years)	Survival, disease recurrence and outcomes in patients with carcinoid tumours are not determined by the surgical procedure but by the size and histological features of the tumour and the status of the regional lymph nodes	Survival: 92% at 5 years 77% at 10 years Disease recurrence: 10.5% (10/95) at the median follow-up of 66 months (unknown in which operative group the recurrences occurred) Operative mortality: 2.4% (3/124) Operative morbidity: No data available	Adequate-sized historical retrospective single-centre study showing that carcinoid tumours are malignant and 10% of patients present with metastases 78 of the 124 tumours resected, 78 (62.9%) were peripheral The authors did not present data for statistical comparison between the lobar and sublobar groups There were insufficient data presented by the authors to comment on whether peripheral carcinoid tumours require a lobectomy		
Hurt and Bates (1984), Thorax, UK [3] Retrospective cohort study (level 2b)	Single-centre retrospective study: Between 1951 and 1983, 62 out of 79 patients had a lobectomy or greater resection, 7 had a segmentectomy or wedge resection, 3 had a bronchotomy and Gebauer skin graft, 4 had a bronchotomy, 2 had enucleation and 1 had no resection It is unknown how many patients had a typical carcinoid Median age: no data	Survival rates and outcomes are acceptable postresection in patients with bronchial carcinoid regardless of the type of surgical intervention	Survival: 94% at 10 years Disease recurrence: 3.2% (2/62) in the lobectomy or greater resection group at 5-30 years follow-up. No recurrence in the segmentectomy/wedge resection group Operative mortality: No operative mortality No operative mortality: No data available	Small historical retrospective single-centre series: Provides data regarding early experience of lung resection for carcinoid and results of follow-up, but little data to compare a lobectomy or greater resection and sublobar resection. The authors concluded that carcinoid tumours may be treated by a bronchotomy or sleeve resection of the bronchus in suitable cases. The authors showed that if serious infective changes have occurred in the lung distal to the tumour or if the tumour has extended into the lung parenchyma (88% of cases in this series), lung resection will be necessary. The group suggested that the follow-up period should be for at least 25 years, in view of the incidence of late recurrence		
Yendamuri <i>et al.</i> (2011), Ann Thorac Surg, USA [4] Retrospective cohort study (level 2b)	Consecutive case series of patients from the Surveillance Epidemiology and End Results database: Between 1973 and 2006 4785 patients with lung cancer and histological codes for carcinoid or atypical carcinoid (patients with another primary cancer excluded); 2681 patients who had a lobectomy or greater resection, 797 had sublobar resection (segmentectomy or wedge resection) Mean age: 53.03 ± 15.53 years in the lobectomy or greater resection group, 59.65 ± 15.27 years in the sublobar resection group	Multivariate analysis showed that sublobar resection of carcinoid tumours did not compromise survival outcomes	Survival: Lobectomy: 84.16 ± 70.4 months Sublobar resection: 67.43 ± 59.2 months (mean survival based on univariate analysis) Disease recurrence: No data available Operative mortality: No data available Operative morbidity: No data available	Multivariate and propensity score matched analysis showed that the extent of resection was not significantly associated with overall survival, whereas age, gender, race and stage are Large retrospective series; however, biases exist between groups. The lobectomy or greater resection group was significantly younger, with less female patients, more with atypical carcinoid and more with nodal disease. However, propensity score multivariate analysis could have corrected the limitation of univariate analysis		

Table 1: Summary table

BEST EVIDENCE TOPIC

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
				The study does not provide the number of peripheral tumours
				It is unknown from the study how many had a preoperative diagnosis of carcinoid
				No data on disease recurrence presented
Ferguson <i>et al.</i> (2000), Eur J Cardiothorac Surg, USA [5] Retrospective cohort study (level 2b)	Multicentre retrospective study: Between 1980 and 1998, 114 out of 145 patients had a lobectomy or greater resection, 3 had sleeve resection without lung resection, 22 had an open segmentectomy or wedge resection and 6 had VATS wedge resection (the 3 sleeve	Sublobar resection of early stages carcinoid tumours did not alter survival, regardless of histological subtype Survival was not better for patients who had a major resection compared with	Survival: Lobectomy: 86% at 5 years Wedge resection: 82% at 5 years ($P = 0.17$) Disease recurrence: 6% (8 patients) at an interval of 42.9 ± 24.9 months	Adequate-sized multicentre retrospective series showing either major lung resection or wedge resection is appropriate treatment for patients with early stage typical bronchial carcinoid tumours We noted that there are some
	resection without lung resection and 6 VATS cases were excluded)	sublobar resection Formal anatomical	Operative mortality: 0.7%	discrepancies in the number of patients in this series
	Out of the total, 80.9% of patients had typical carcinoid	long-term outcomes in patients with an atypical subtype as local recurrence	Operative morbidity: 15.6 % had pulmonary complications, 6.7% had	The authors did not explain the reasons behind excluding the 6 VATS segmentectomy o wedge resection cases from
	Mean age: 56.5 ± 15.2 years	is more common	cardiovascular complications and 12.4% had other complications	the analysis. Proportional hazard analysis of survival using the covariates of age, sex, histology and type of operation demonstrated that the important covariate was age (and possibly histology). The authors commented that due to the fact that there was only a small number of patients with atypical histolog or who underwent sublobar resection, the findings should not be considered as conclusive evidence of the lack of difference in survival
Cardillo <i>et al.</i> (2004), Ann Thorac Surg, Italy [6] Retrospective cohort study (level 2b)	Single-centre retrospective study: Between 1990 and 2002, 153 out of 163 patients had a lobectomy or greater resection, 10 had a segmentectomy or	The type of surgical resection does not influence survival rates, recurrence or outcomes	Survival: Lobectomy or greater resection: 92.9-100% (based on surgery) at 5 years Segmentectomy and wedge resection: 100%	Large retrospective single-centre study: We noted that only a small number of sublobar resection were carried out and thus statistical comparison of outcomes between the lobectomy or greater resectio and sublobar resection is difficult
	Wedge resection Out of the total, 74.2% (121) had typical carcinoid		Disease recurrence: 1.4% (2/137) of the lobectomy or greater resection group had metastatic disease	
	Mean age: no data		No recurrence in the wedge resection or segmentectomy group at the median follow-up of 54 months	
			Operative mortality: No operative mortality	
			Operative morbidity: 14.2% in the whole group	
Chen <i>et al.</i> (2010), Interact CardioVasc	Single-centre retrospective study:	The type of surgical resection does not	Survival: 0% at the median follow-up of	Very small series with only two of the tumours (25%)

Continued

Author, date, journalPatient groupOutcomesKey resultsand countryStudy type(level of evidence)	Comments
Surg, Japan [7] Between 2000 and 2009, 7 out of 8 patients had a influence survival rates, recurrence or outcomes 33 months (6-68 m Disease recurrence) Retrospective cohort study lobectomy or greater resection and 1 had a segmentectomy Disease recurrence) All patients had typical carcinoid All patients had typical carcinoid Segmentectomy: 09 months Median age: 48 years Operative mortality No operative mortality No data available	e: Insufficient number of patients (1/7) at 68 to make a valid comparison. The authors concluded that a % at 68 typical carcinoid might require a major surgical procedure, which we think is invalid, y: considering the data ality presented
Bini et al. (2008), Interact CardioVasc Thorac Surg, Italy [8]Single-centre retrospective study: Between 1986 and 2006, 44 out of 54 patients had a lobectomy or greater resection, 8 had a segmentectomy or wedge resection and 2 had a sleeve bronchial procedure without lung resectionType of surgical intervention may influence survivalSurvival: Lobectomy: 96% at Pneumonectomy: 5 yearsOut of the total, 45 (83.3%) had typical carcinoidOut of the total, 45 (83.3%) had typical carcinoidOperative mortality No operative mortality No data available	54% at 5patients with peripheral tumours showing good results100% at 5at mid- and long-term survivalNo statistical testing reported for the difference in survival based on the type of resectiony:No data comparing outcomes between a lobectomy or greater resection and sublobar
Rea et al. (2007), Eur J Cardiothorac Surg, USA [9]Single-centre retrospective study: Between 1968 and 2005, 149 out of 252 patients had a lobectomy or greater resection, 27 had a segmentectomy or wedge resection and 76 had sleeve or bronchoplastic proceduresSublobar resection provides better outcomes in patients with typical carcinoid and N0 statusSurvival: Univariate analysis Lobectomy: 64,6% at Pneumonectomy: 6 years Segmentectomy or resection: 80.8% at (P = 0.003)Of the total, 174 (69.0%) had typical carcinoidOf the total, 174 (69.0%) had typical carcinoidDisease recurrence: 7.9% at the median of 121 months in th groupMedian age: 45 years (8-79 years)Operative mortality No operative mortality No operative mortality operative mortality no operative mortality No operative mortality No operative mortality No operative mortality	at 10 years60% at 1060% at 1010 yearsr wedger wedger wedge10 yearsMultivariate analysis showed a significant prognostic factor10 yearsMultivariate analysis showed a significant prognostic value for histology, nodal status, age and sex. However, there is no multivariate data table showing the relative importance of each potential prognostic factory:alityAlthough it is valid to state ty:that histology and nodal status
Toledo et al. (1989), Eur J CardiothoracSingle-centre retrospective study:Sublobar lung resection provides similar outcomes to lobar resectionSurvival: Lobectomy or great resection: 96.5% at Segmentectomy or resection 7 had asegmentectomy or wedge resection and 8 had bronchial resectionsSublobar lung resection provides similar outcomes to lobar resectionSurvival: Lobectomy or resectionToledo et al. (1989), Survival: Lobectomy or great resectionSingle-centre retrospective study: greater resection 7 had asegmentectomy or wedge resectionsSublobar lung resection provides similar outcomes to lobar resectionSurvival: Lobectomy or resectionVery Spain [10]Between 1974 and 1987, 29 out of 45 patients (44 cases included) had a lobectomy or greater resection 7 had asegmentectomy or wedge resectionsDisease recurrence: At the mean follow months:	 53 months wedge We noted that although there 53 months were no local recurrences, the disease recurrent rate was e: higher in the segmentectomy

Table 1: (Continued)

Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	All cases were typical carcinoid Median age: 44 years (23-76 years)		Lobectomy or greater resection: 3.4% (1/29) at 53 months Segmentectomy/wedge resection: 14.3% (1/7) Operative mortality: No operative mortality Operative morbidity: Lobectomy or greater resection: 15.8% Segmentectomy, wedge or bronchoplastic resection: 24%	There is an insufficient number of sublobar resections to compare outcomes against lobectomy or greater resection to draw conclusions regarding lung parenchymal preservation. No statistical analysis was carried out to compare outcomes in lobar and sublobar resection groups
Abdi <i>et al.</i> (1988), J Surg Oncol, Canada [11] Retrospective cohort study (level 2b)	Single-centre retrospective study: Between 1960 and 1986, 6 out of 11 patients (10 included) had a lobectomy and 4 had wedge resection Of the total, 81.8% had typical carcinoid Mean age: 60.2 years	Lobectomy or wedge resection can provide a suitable surgical treatment for patients with carcinoid tumours	Survival: 100% up to 3.27 years in both groups Disease recurrence: 0% in both groups up to 3.27 years Operative mortality: No operative mortality Operative morbidity: No data available	Very small retrospective series. Only 2/10 patients operated on had nodal disease The results from this series are insufficient to comment on whether peripheral carcinoid tumours require a lobectomy

Table 1: (Continued)

and nodal spread as important prognostic factors for diseasefree survival [4, 5]. Cardillo *et al.* [6] reported a higher nodal metastasis rate with an atypical carcinoid (62.48% with atypical carcinoid vs 11.57% with typical carcinoid), which was associated with a significantly worse prognosis. The authors recommended a formal anatomical resection with radical mediastinal lymphadenectomy in all patients in order to allow accurate staging. However, Ferguson *et al.* [5] suggested that limited resection with lymph node dissection should be considered for peripheral tumours that are early stage and typical histology since local recurrence is unlikely and the prognosis is excellent.

Yendamuri et al. [4] retrospectively reviewed a series of 3478 cases (2681 lobectomy or greater resection, 797 sublobar resection) extracted from the Surveillance Epidemiology and End Results database between 1973 and 2006. Multivariate analysis in the overall group and propensity score matched analysis for patients with a typical carcinoid showed that the extent of resection was not significantly associated with overall survival. Both models showed that age, female gender, race and stage were associated with overall survival. As a retrospective series, there was a selection bias demonstrated, with the lobectomy or greater resection group being significantly younger, with less female patients, more with an atypical carcinoid and more with nodal disease. The exact type of operation, and the number of peripheral tumours and patients with a preoperative diagnosis of carcinoid were not known. In addition, detailed preoperative comorbidity data and the postoperative staging were not known, with no data being presented on either disease recurrence or operative mortality and morbidity. In spite of the conclusions of the paper, it is difficult to draw definitive

conclusions on long-term survival with the bias of a retrospective study.

Ferguson et al. [5] retrospectively reviewed a multicentre series of 142 cases (90 lobectomies, 20 bilobectomies, 4 pneumonectomies, 22 open segmentectomies/wedge resections, 6 VATs segmentectomies/wedge resections). Follow-up was available for 89% of patients to mortality or the end of the time period. Limited resection was considered for all peripheral tumours that were early stage and with typical carcinoid histology. Multivariate Cox proportional hazards analysis of recurrence-free survival showed that the histological subtype was the only significant predictor of recurrence-free survival at 5 years (90% for typical carcinoid vs 70% for atypical carcinoid, P = 0.021). There was no significant difference in disease-free survival between those with major resection and minor resection. However, only the 22 open segmentectomies/wedge resections were included in the analysis. In addition, there were discrepancies in the number of patients within and between the data tables. Considering the low number of patients with sublobar resection, it is difficult to compare outcomes between a lobectomy or greater resection and sublobar resection.

The other studies presented [2, 3, 6, 7] are retrospective singlecentre series following up patients with pulmonary carcinoid, rather than comparing outcomes between a lobectomy or greater resection and sublobar resection. The surgical strategy varied between a conservative approach with lung parenchyma conservation or only choosing a sublobar resection in cases where preoperative pulmonary function tests precluded conventional resection [5, 6, 8-10]. The number of patients with peripheral tumours ranged between 22.6% [10] and 100% [7] and the number of patients with a preoperative diagnosis of carcinoid ranged between 51.9% [9] and 86.7% [11], with many series not providing either or both of these data. As a result, a lobectomy or greater resection was necessary on anatomical or diagnostic grounds and led to a low number of sublobar resections in these series. No series compared postoperative morbidity between lobectomy or greater resection and sublobar resection. Owing to the high heterogeneity within and between series, small numbers of peripheral tumours and low reporting rates of disease recurrence and postoperative morbidity, it is difficult to draw conclusions.

There is a lack of comprehensive randomized studies to compare a lobectomy or greater resection and sublobar resection. Although a typical carcinoid is reported as having good long-term disease-free prognosis, there is little objective evidence to show the equivalence or superiority of a lobectomy over sublobar resection in terms of disease recurrence and longterm survival. With an atypical carcinoid, there is insufficient data that can be used for evidence-based practice.

CLINICAL BOTTOM LINE

Although a typical (low-grade) carcinoid is reported as having good long-term disease-free prognosis especially without nodal disease, there is little objective evidence to show the equivalence or superiority of a lobectomy or greater resection over sublobar resection in terms of disease recurrence and long-term survival. With an atypical carcinoid, there is insufficient data that can be used for evidence-based practice.

There is a tendency for sublobar resections to be performed in either early stage typical carcinoid patients or patients with preoperative pulmonary function tests that preclude conventional resection. Further randomized studies are needed to assess the postoperative morbidity, long-term survival and disease recurrence between the two approaches.

This current review of the literature suggests that sublobar resection with lymph node dissection for accurate staging can be sufficient for patients with a typical carcinoid. In the case of an atypical carcinoid, the surgical strategy should be based on the lesion and lymph node involvement, and each patient should be assessed fully and apprised by a multidisciplinary team.

Conflict of interest: none declared.

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eComment. The definition of neuroendocrine tumour and sublobar resection

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We read with great interest the article by Afoke and colleagues [1]. The authors addressed the question whether a sublobar resection might be equivalent to a lobectomy for surgical management of peripheral carcinoid tumours of the lung. We would like to comment on two important issues with regard to carcinoids and sublobar resections.

Carcinoids are a subgroup of non-small cell lung cancer (NSCLC) with neuroendocrine differentiation according to the World Health Organization (WHO) classification system [2]. A combination of morphologic features, mitotic rate and absence or presence of necrosis are used to classify neuroendocrine tumours [3]. Often, video-thoracoscopic wedge resection is attempted in patients with a peripherally-located pulmonary lesion, if the lesion is more likely to be malignant. The surgical management then depends on the results of the frozen section. The differentiation between atypical carcinoids and large cell neuroendocrine tumours of the lung. Thus, the intraoperative decision making process for the appropriate oncological treatment can be difficult.

Carcinoids should be dealt with like NSCLC. Thus, sublobar resections should be avoided in patients who can tolerate lobectomies [4]. The term sublobar resection might be too imprecise. Sublobar resections may refer to wedge resections or anatomical segmentectomies. If sublobar resections are carried out, segmentectomies are associated with significantly better cancer-related survival than wedge resections in stage IA NSCLC [5]. In this context, it could be helpful to utilize precise terms and definitions of the surgical resection, so that there is no room for possible misinterpretations or under-treatment.

Conflict of interest: none declared.

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eComment. Surgical management of carcinoid tumours of the lung: sublobar resection versus lobectomy

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Afoke and coworkers recently addressed the following question 'Is sublobar resection equivalent to lobectomy for surgical management of peripheral carcinoid?' [1]. Using a search strategy based on keywords 'carcinoid tumour' and 'pulmonary surgical procedures' the authors selected 10 articles to provide the best evidence to answer the question. Since the classification into two distinctive forms, typical (TC) and atypical carcinoids (AC), has changed over the years, this selection is, however, questionable. Indeed, in 1998, Travis and coworkers proposed new criteria for AC and its separation from TC. Based on these new criteria, the World Health Organization (WHO) established a definitive classification of pulmonary neuroendocrine tumours in 1999, which was confirmed in 2004. Consequently, in series of carcinoid tumours classified according to the old classifications (before 1999) there are some overlaps among the two entities (TC vs AC) in comparison with the definitive classification, leading to possible misleading factor in the Afoke and coworkers' study. In our opinion the series published before 1999 might be discarded to determine the long-term survival and disease recurrence such as we had done in a previous study in the field [2]. In fact, in the Afoke and coworkers' selection, there are only three valuable articles to address the question: the article by Chen and coworkers reporting a small group of patients included between 2000

and 2009 [1]; and two articles including patients before 1999, in which the pathology slide blocks were reviewed for reclassification according to the 1999 WHO criteria for neuroendocrine tumours [3, 4]. Finally, despite this limitation, the Afoke and coworkers' conclusion is in line with a recent study conducted in a large series of patients, in which the authors stated that 'compared with lobectomy, sublobar resection is associated with non-inferior survival in patients with typical carcinoid of the lung' [5].

Conflict of interest: none declared.

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