

Does surgery improve prognosis in patients with small-cell lung carcinoma?

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Received 11 September 2012; received in revised form 13 October 2012; accepted 22 October 2012

Abstract

A best evidence topic was written according to a structured protocol, asking 'does surgery improve prognosis in patients with small-cell lung carcinoma (SCLC)?' One hundred and thirteen papers were identified, of which the nine papers best able to answer the question were selected and the details of each tabulated. The prohibitive attitude of clinicians toward surgery in SCLC has prevailed since the 1960s, informed by a prospective randomized trial in which 144 patients were assigned to surgical treatment or to radical radiotherapy. Surgery conferred no survival benefit when compared with radical radiotherapy as assessed at 6 monthly intervals up to 10 years post-treatment. Patients with metastatic disease were excluded; however, diagnostic advances subsequent to these trials justify a re-evaluation of the issue, given the greater degree of accuracy with which sub-groups of patients who might benefit from surgery can now be defined. Only one further prospective, randomized trial features in the literature. This study also discerned that no survival benefit was accrued by adding surgery to chemotherapy. However, this study only included patients who responded to an initial course of chemotherapy and also excluded patients with peripheral nodules only. Subsequent investigators have asserted the value of surgery in SCLC. A retrospective case-control study found that surgery significantly improved median survival in patients with stage I disease when compared with patients undergoing medical therapy. One British centre reported survival rates of 52% at 5 years amongst patients undergoing resection and nodal dissection for stage II-IIIa disease. In a retrospective analysis of the Norwegian cancer database, 5-year survival for patients with stage I undergoing surgery was 44.9%, as opposed to 11.3% amongst those treated medically. This finding was echoed in the analysis of the surveillance epidemiology and end results database in the USA, which found improved median survival amongst patients undergoing surgery for limited SCLC. Prospective studies of carefully selected patients have documented good median survival in patients whose tumour was completely resected. We conclude that surgery for early-stage SCLC improves prognosis as part of a multi-modality approach. This echoes the advice of the 2011 national institute of health and clinical excellence guidelines regarding surgery in SCLC.

Keywords: Small cell lung cancer • Surgery

INTRODUCTION

A best evidence topic was constructed according to a structured protocol [1].

THREE-PART QUESTION

In [patients diagnosed with small-cell lung carcinoma (SCLC)] does [surgical resection] result in a [better prognosis]?

CLINICAL SCENARIO

During a lung cancer multi-disciplinary meeting, a patient with a 2-cm peripheral nodule on his chest X-ray is discussed. Tissue from a computed tomography (CT)-guided biopsy provides a histological diagnosis of small-cell lung cancer. Discussion breaks out as to whether surgery is indicated in the absence of any

metastasis, and unsure as to the likely results of resection in this patient you resolve to check the literature.

SEARCH STRATEGY

Medline 1948-present using the PubMed interface ((small cell and small-cell)) not non-small.m_titl AND lung.m_titl AND (surgical or surgery or resection).m_titl, limited to human.

SEARCH OUTCOME

One hundred and thirteen papers were found using the reported search, and the nine papers best able to answer the clinical question identified.

RESULTS

Fox and Scadding [2] conducted a randomized controlled trial of 144 patients from 29 surgical centres in the UK who had been

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Fox and Scadding (1973), <i>Lancet</i> , UK [10] Prospective randomized controlled trial (level II)	One hundred and forty-four patients from 29 centres in the UK diagnosed with small-cell lung carcinoma on bronchial biopsy. Patients who were deemed unfit for surgery or who showed evidence of extrathoracic metastases or inoperable tumour were excluded from the study. Seventy-one allocated to surgery, 73 to radical radiotherapy	Mean survival Survival data recorded at 6 monthly intervals to 5 years, annually to 10 years	Mean survival 199 days for the surgical arm, 300 days for the radiotherapy arm Survival superior in the latter group, $P = 0.04$. Only one surgical patient survived to 5 years, and none beyond that	This study predates the advent of CT scanning and of mediastinoscopy, so there is room for doubt with respect to patient selection within the study. Furthermore, the analysis is by intention to treat, so that several patients who underwent either exploratory thoracotomy only or no surgery at all have been included in the surgical arm of the trial. In all patients who underwent surgery, a pneumonectomy was performed, which may itself accrue excess morbidity and mortality
Lad <i>et al.</i> (1994), <i>Chest</i> , Multinational [3] Prospective randomized controlled trial (level II)	Three hundred and twenty-eight patients with a bronchoscopic diagnosis of SCLC were administered with five cycles of cyclophosphamide/doxorubicin/vincristine chemotherapy. Patients with extra-hemithoracic disease spread, supraclavicular node involvement or cytologically-positive pleural effusions were excluded, as were patients with peripheral nodules and normal bronchoscopies. Two hundred and seventeen patients achieved at least partial objective response to chemotherapy, and it was this group who were then randomized to surgical and non-surgical arms	Median survival	Median survival 15.4 months for the surgical arm, 18.6 months for non-surgical. No benefit for surgery found	This study excludes those patients who most likely benefit from resection, namely those patients with peripheral nodules. As the authors acknowledge, such nodules may have a somewhat different natural history from other more diffuse forms of SCLC. The randomization of only those patients who have responded to a period of chemotherapy also introduces problems. The chemotherapy regime adopted predates more efficacious platinum-based therapies, and therefore may represent an interval during which fast-growing tumour may progress irrespective of its improved appearance in terms of clinical staging. This is borne out by the fact that 17% of patients allocated to the surgical arm had irresectable tumour, which correlated to the pre- but not post-chemotherapy T staging of these patients. Four patients undergoing surgery also had an incomplete resection
Karrer and Ulsperger (1995), <i>Acta Odontol</i> , Multinational [4] Prospective cohort study (level III)	A prospective multicentre trial of 183 consecutive patients who were staged as T1-2N0M0 based on X-ray, CT and mediastinoscopy, and then underwent complete resection. No randomization with respect to surgery occurred, although patients were randomized to one of the three adjuvant chemotherapy regimes	Survival by stage (measured at 1, 12, 30 and 48 months) Survival by completeness of resection Survival by chemotherapy regime	63% 30-month survival for completely-resected TN0M0 disease 37% for TN2M0 disease 44% 3-year survival rate for all completely-resected disease, 19% for incompletely-resected No significant difference between regimes	The indications for surgery as first step should be the same in early SCLC as for other lung cancers

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Table 1: (Continued)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Eberhardt <i>et al.</i> (1999), Br J Cancer, Germany [5] Prospective cohort study (level III)	Prospective trial of multimodal treatment for patients with SCLC stage IB–IIIB, excluding patients with T1 N0 (IA) disease. Forty-six consecutive patients who enrolled for treatment at one centre were extensively worked up, with staging investigations including CT scanning of the chest, upper abdomen and brain; abdominal ultrasound, radionuclide bone scan, bronchoscopy and mediastinoscopy. Patients with stage IB/IIA disease were allotted to a programme of four cycles of cisplatin/etoposide neoadjuvant chemotherapy. Patients with stage IIB/IIIA disease received an additional course of radiotherapy. Once their respective treatments had been completed, both groups underwent restaging, with repeat mediastinoscopy in patients with node positive disease. Patients who were node-negative proceeded to surgery, whilst those with persistent mediastinal disease received further irradiation	Median survival Survival by stage Relapse pattern	Overall median survival 36 months. Median survival in patients with complete resection 68 months No significant difference in survival between the groups involved 36% of patients who underwent complete resection experienced distant relapse. No local recurrence	In the context of maximally rigorous staging and preoperative chemoradiotherapy, good results for complete resection can be achieved even in quite advanced cases of SCLC
Rostad <i>et al.</i> (2004), Eur J Cardiothoracic Surg, Norway [6] Case series (level IV)	Retrospective review of all cases of SCLC recorded in Norway between 1993 and 1997. A total of 2442 patients were reviewed, of which 38 underwent surgery. All of the latter patients were staged preoperatively as Ia–Ib. Of those patients who did not receive surgery, 697 had either limited disease according to the VALSG criteria or were of unknown stage. These patients were then retrospectively re-staged, yielding 142 patients with stage I disease of which 31 were found to have contraindications to surgery, leaving 111 patients who might conceivably have had surgery for stage I disease but had conventional chemoradiotherapy instead	Five-year survival rates in patients with stage I disease (too few patients underwent surgery for more advanced disease to draw significant conclusions)	In patients with stage I disease, the 5-year survival in the surgical group was 44.9 vs 11.3% in the conventionally treated group. This represents a significant difference ($P < 0.05$)	Patients with peripherally located tumour should be referred for surgery, given the improved long-term survival rates
Badzio <i>et al.</i> (2004), Eur J Cardiothoracic Surg, Poland [7] Individual case– control study (level III)	Retrospective comparative case–control analysis of the 76 patients who underwent surgical resection for SCLC at one institution between 1984 and 1996. Seven patients had inadequate information on	Median survival Survival by stage	Median survival 22 months for patients undergoing surgery, 11 months for those not undergoing surgery ($P < 0.01$) Median survival times were significantly better for surgical	Three independent predictors of survival were noted: surgical treatment, female sex and freedom from involvement of regional lymph nodes. These findings suggest the value of a surgical

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Table 1: (Continued)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	preoperative staging, and a further two could not be satisfactorily matched with medically treated patients. The remaining 67 patients were matched with patients who underwent non-surgical treatment in terms of T and N stage, sex and performance status	Local and distant relapse rates	patients in the cT1 (28 vs 12 months), cT2 (22 vs 10 months), cN0 (28 vs 13 months) and cN1 (18 vs 11 months) groups. A survival advantage was noted in the cN2 group (19 vs 9 months), but this did not reach the level of statistical significance Local relapse was less likely in post-surgical patients ($P < 0.01$), but distant relapse rates were similar across both the groups	approach to SCLC, notwithstanding the limitations of a retrospective study—as the authors themselves point out, there is a variation between the groups in terms of the regimes of chemotherapy and radiotherapy received, some of which would now be regarded as sub-optimal
Brock <i>et al.</i> (2005), J Thorac Cardiovasc Surg, USA [8] Retrospective review (level IV)	Retrospective review of 1415 patients with SCLC treated at one institution between 1976 and 2002, of whom 82 had undergone surgery with curative intent. Most patients did not have a confirmed diagnosis of SCLC preoperatively, and underwent surgery as treatment for a suspicious pulmonary nodule. Disease stage was retrospectively classified according to the pTNM system, and verified contemporaneously by a pathologist who reviewed the intraoperative samples. Treatment consisted of surgery alone (11%), surgery with neoadjuvant therapy (22%) or surgery with adjuvant therapy (55%)	Five-year survival Survival by stage Survival by platinum vs non-platinum chemotherapy Survival by type of surgery	Five-year survival for the whole cohort was 42% Survival of patients with stage I disease was significantly better than that of patients with stage II, III or IV disease (58 vs 18, 23 and 0%, respectively, $P < 0.01$) Five-year survival of patients who underwent adjuvant chemotherapy was significantly better in patients who received platinum when compared with non-platinum regimes (68 vs 32.2%, $P = 0.04$). In patients with stage I disease who underwent platinum-based therapy, a 5-year survival rate of 86% was achieved Five-year survival significantly better for those undergoing lobectomy vs more limited surgery ($P = 0.03$)	Highly selected patients with SCLC may benefit from surgery and adjuvant chemotherapy, particularly if chemotherapy is platinum-based
Lim <i>et al.</i> (2008), J Thorac Oncol, UK [9] Retrospective review (level IV)	Retrospective review of 59 patients undergoing surgery for SCLC at one centre, 1980–2006	Survival at 1 and 5 years Survival by preoperative staging	Overall survival at 1 and 5 years was found to be 76 and 52%, respectively Clinical staging ranged from IA to IIIB. No correlation of survival with either clinical or pathological staging was observed	Good survival rates were attained for patients with stage I–III disease who underwent surgery with nodal dissection. However, the authors acknowledge that ‘open and close’ cases were excluded, and consistency in adjuvant treatment across the period was lacking
Schreiber <i>et al.</i> (2010), Cancer, USA [10] Retrospective review (level IV)	Retrospective analysis of the SEER database. Fourteen thousand one hundred and seventy-nine patients were diagnosed with limited SCLC in the period 1988–2002, of which 863 underwent surgery	Median survival Effect of surgery type on survival	Surgery was associated with improved median survival for both localized and regional disease: from 15 to 42 and 12 months to 22 months respectively ($P < 0.01$) Patients undergoing lobectomy for localized disease had a median survival time of 65 months, for regional disease 25 months. This compares favourably with patients undergoing pneumonectomy,	The use of surgery, and particularly, lobectomy in patients with limited SCLC was associated with improved survival

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Table 1: (Continued)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
			sublobar resection or no surgery ($P < 0.01$)	
		Effect of surgery on lymph node status	Surgery improved median survival in N0, N1 and N2 disease ($P < 0.01$)	

SEER: surveillance epidemiology and end results; VALSG: veterans administration lung study group.

diagnosed with SCLC on bronchial biopsy, who were allocated to treatment with either surgery or radical radiotherapy. The mean survival time of the former group was 199 days, of the latter 300 days—a statistically significant disparity ($P = 0.04$). The authors concluded that surgery was not a useful intervention in cases of SCLC.

Lad *et al.* [3] conducted a randomized controlled trial during which 328 patients with a bronchoscopic diagnosis of limited SCLC were administered with five cycles of chemotherapy. Two hundred and seventeen patients achieved some objective response to chemotherapy, and it was this group who were then randomized to surgical and non-surgical arms. The authors reported a median survival of 15.4 months for the surgical arm and 18.6 months for the non-surgical arm, and hence concluded that surgery is of no benefit in patients with limited SCLC.

Karrer and Ulsperger [4] undertook a prospective multi-centre trial of 183 consecutive patients who were staged as T1-2N0M0 and underwent complete resection. No randomization with respect to surgery occurred. A 4-year survival rate of 57% was reported in patients with pT1-2N0M0 disease ($P = 0.0062$). Furthermore, encouraging 4-year survival rates were found in those patients whose staging was upgraded post-surgery: 34% in pT1-2N1 M0 disease, 33% in pT1-2N2M0 disease.

Eberhardt *et al.* [5] performed a prospective trial of multi-modal treatment for patients with SCLC stage IB–IIIB, excluding patients with T1 N0 (1A) disease. Forty-six consecutive patients who enrolled for treatment at one centre received endoscopic and radiological work-up. Patients with stage IB/IIA disease were allotted to a programme of neoadjuvant chemotherapy, whereas patients with stage IIB/IIIA disease received an additional course of radiotherapy. Patients were then re-staged, and those who were node-negative proceeded to surgery, whilst those with persistent mediastinal disease received further irradiation. Twenty-four patients proceeded to surgery, one of whom was found to have multiple pleural metastases on table and therefore did not undergo resection. Therefore, a total of 23 patients underwent complete resection. Within this group, a median survival of 68% and a 5-year survival of 63% were noted (Table 1).

Rostad *et al.* [6] retrospectively reviewed all cases of SCLC recorded in Norway between 1993 and 1997, in an attempt to establish whether surgery might have been beneficially offered to a greater number of patients. A total of 2442 patients were reviewed, of which 38 underwent surgery. All of the latter patients were staged preoperatively as Ia–Ib. The 5-year survival in this group was 44.9%, in contrast to 11.3% in stage I patients who underwent conventional treatment. The authors concluded

that patients with stage I SCLC and a peripherally located tumour should be referred for surgery.

Badzio *et al.* [7] undertook a retrospective case-control analysis of the 76 patients who underwent surgical resection for SCLC at one institution between 1984 and 1996, who were matched with patients who underwent non-surgical treatment in terms of T and N stage, sex and performance status. The median survival times were significantly better for surgical patients in the cT1 (28 vs 12 months), cT2 (22 vs 10 months), cN0 (28 vs 13 months) and cN1 (18 vs 11 months) groups.

Brock *et al.* [8] reviewed the 1415 patients with SCLC treated at one institution between 1976 and 2002, of whom 82 had undergone surgery with curative intent. Treatment consisted of surgery alone (11%), surgery with neoadjuvant therapy (22%) or surgery with adjuvant therapy (55%). The authors found that overall 5-year survival for the whole cohort was 42%. Survival of patients with stage I (T1–2 N0M0) disease was significantly better than that of patients with stage II, III or IV disease (58 vs 18, 23 and 0%, respectively, $P < 0.01$).

Lim *et al.* [9] reviewed 59 cases of SCLC who had undergone surgical resection at one centre between 1980 and 2006, of whom 20 had had a preoperative diagnosis. No patient had received neoadjuvant chemotherapy. Survival at 1 and 5 years was found to be 76 and 52% respectively, with no correlation to clinical or pathological staging.

Schreiber *et al.* [10] identified 14 179 patients within the SEER population-based database who had been diagnosed with limited SCLC between 1988 and 2002. Of these, 863 patients underwent surgery, which conferred a benefit in median survival when compared with the non-surgical group—28 vs 13 months. The 5-year survival for patients undergoing surgery was 34.6, and only 9.9% amongst those who did not ($P < 0.01$). Lobectomy was associated with the best outcome in terms of survival ($P < 0.01$).

CLINICAL BOTTOM LINE

Surgery is indicated for patients with stage I or II SCLC after full preoperative assessment which would optimally include mediastinoscopy; however, patients with stage III disease are unlikely to benefit from surgery. Adjuvant chemotherapy should also be discussed. These conclusions reiterate the guidelines issued by national institute of health and clinical excellence in 2011 that surgery should be considered 'in patients with early-stage SCLC (T1-2a, N0, M0)' [11]. These guidelines also advocate that SCLC

determined by the intraoperative frozen section of a resected nodule should mandate conversion to lobectomy; however, the evidence for this assertion is not assessed in this paper.

Conflict of interest: none declared.

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