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REVIEW

A meta-analysis of the impact of bronchial stump coverage on the risk of bronchopleural fistula after pneumonectomy

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Abstract

The occurrence of bronchopleural fistula (BPF) after pneumonectomy is associated with high morbidity and mortality. The incidence of BPF in historical patients not subjected to bronchial stump coverage (BSC) was between 6 and 12% after pneumonectomy for lung cancer surgery or benign disease. BSC is considered an important prophylactic measure against BPF and is widely used, but its efficacy remains unknown. Our aim was to systematically review the literature, in order to quantify BPF risk in patients receiving or not receiving BSC with any tissue after pneumonectomy. We performed a systematic review in PubMed, for papers published between 1999 and 2012, analysing series of patients treated with pneumonectomy and including both patients receiving coverage and patients not receiving coverage. Both randomized and non-randomized series were eligible. Proportion of failures (i.e. BPF) was analyzed separately in the two groups (patients receiving BSC and patients not receiving BSC). For each study and for the overall series, 95% confidence interval (CI) (without continuity correction) of the observed proportion was calculated. Overall, 21 series were eligible, with 3879 patients (1774 receiving BSC and 2105 not receiving coverage). The decision to perform or not the BSC was randomized only in one small trial, limited to diabetic patients, showing a significant reduction of BPF in favour of coverage. In the 20 remaining studies, baseline risk of BPF in the group of patients receiving BSC and in the group of patients who did not receive coverage was different. In patients receiving coverage, the proportion of BPF was 6.3% (95% CI: 5.3–7.5%). In patients not receiving coverage, the proportion of BPF was 4.0% (95% CI: 3.2–4.9%). In recently published series, the vast majority of patients considered at high risk for BPF received BSC. This common practice hinders an unbiased estimate of the efficacy of BSC in reducing BPF risk. Results of this meta-analysis show that, despite a clear negative selection, the incidence of BPF in patients considered at high risk and receiving coverage was only slightly higher compared with patients considered at low risk and not covered. A randomized trial would help answer the question.

Keywords: Systematic review • Bronchopleural fistula • Bronchial stump coverage • Pneumonectomy

INTRODUCTION

After pneumonectomy, bronchial stump coverage (BSC) is usually advised in high-risk patients to prevent the occurrence of bronchopleural fistula (BPF), a complication that may carry up to a 50% mortality rate [1, 2]. In the survivors, post-pneumonectomy BPF portends multiple operations, prolonged hospitalizations and increased social costs.

As a rule, the perception of high risk for BPF after pneumonectomy is based on the coexistence of widely accepted factors (i.e. neoadjuvant chemoradiotherapy, tuberculosis) that mandate preventative coverage of the bronchial stump.

We reviewed the recent literature in order to quantify the risk of BPF in patients receiving or not receiving BSC with any tissue after pneumonectomy.

METHODS

All the analyses were conducted according to four prespecified steps: (i) definition of the outcomes (definition of the question the analysis was designed to answer); (ii) definition of the trial selection criteria; (iii) definition of the search strategy and (iv) description of the statistical methods used for pooled analysis.

Definition of the outcome

The selected outcome was the occurrence of BPF after pneumonectomy. The aim of this work was to perform a systematic review and meta-analysis of the recent surgical literature, in order to quantify the risk of BPF in patients receiving or not receiving BSC with any tissue after pneumonectomy.

Trial identification criteria

All original reports (randomized clinical trials, prospective series, retrospective series), published between 1999 and 2012, in which outcome of patients treated with pneumonectomy was described, were eligible, if both patients receiving coverage and patients not

receiving coverage were included. Only papers published in peer-reviewed journals and in English were considered.

Search strategy

Deadline for trial publication and/or presentation was December 2012. Search was performed through Medline (PubMed: www.ncbi.nlm.nih.gov/PubMed). Keywords used for searching were pneumonectomy, BPF, empyema, thoracostomy. In addition to computer browsing, reviews and original papers were also scanned in the reference section to look for further reports.

Data extraction

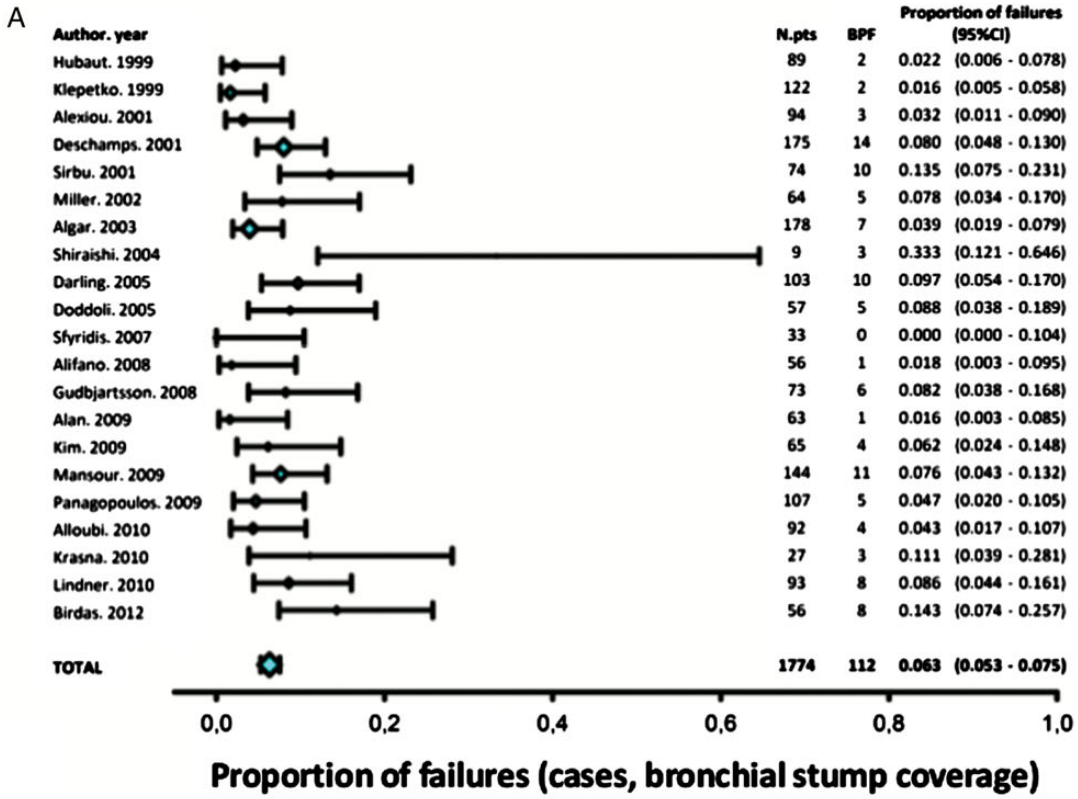
The last available update of each trial was considered as the original source. The following data were extracted for each publication: (a) year of publication; (b) total number of cases; (c) description of criteria used for performing BSC or not; (d) number of patients who did not receive BSC; (e) number of failures (BPF) in patients who did not receive BSC; (f) number of patients who received BSC; (g) number of failures (BPF) in patients who received BSC. All data were reviewed and separately computed by two investigators (G.R. and M.D.M.).

Data synthesis

Due to the non-randomized assignment to treatment groups (both randomized and non-randomized series were eligible) and the different baseline risk of BPF in the two groups, a formal comparison between patients receiving BSC and patients not receiving BSC was not performed, and proportion of failures (i.e. BPF) was analysed separately in the two groups. For each study and for the overall case series, the 95% CI (without continuity correction) of the observed proportion was calculated. In the figures, the derived results are

Table 1: Criteria for bronchial stump coverage after pneumonectomy reported in each publication

Author, year of publication	Criteria for bronchial stump coverage
Hubaut *et al.* (1999) [1]	Not specified
Klepetko *et al.* (1999) [2]	Criteria unclear. In 50 patients, a generous pedicled flap of the anterior pericardium with or without the phrenic vessels was used. This technique was applied irrespectively whether the pericardium had been opened during the resection procedure, and in general was chosen in all patients considered to be at a high risk for development of fistula, i.e. patients with any form of neoadjuvant therapy or extended resections
Alexiou *et al.* (2001) [3]	The main bronchus was simply stapled in 112 patients (54%) and reinforced with a pedicled pleural flap in 94 cases (46%), the difference relating to operator preference only
Deschamps *et al.* (2001) [4]	Not specified
Sirbu *et al.* (2001) [5]	On the right side, the pneumonectomy stump was covered with mediastinal pleura and a pericardial fat pad. Primary intercostal muscle or pericardial flap was used only in high-risk cases
Miller *et al.* (2002) [6]	Not specified
Algar *et al.* (2003) [7]	The bronchial stump was covered with autologous tissue in 178 cases (74%)—in 88% of right pneumonectomies and 64% of left pneumonectomies. This coverage was performed more frequently in those cases more likely to develop a BPF (right pneumonectomies, older patients, those who had previously taken immunosuppressive drugs); however, the final decision of whether to cover the bronchus was made by the operating surgeon
Shiraishi *et al.* (2004) [8]	Not specified
Darling *et al.* (2005) [9]	Not specified
Doddoli *et al.* (2005) [10]	The bronchial stump was reinforced in 57 patients with a pedicled parietal pleural flap in 25 patients, mediastinal fatty tissues from the thymic area in 14 patients, a pedicled muscle in 15 patients and pericardium in 3 patients, with the difference relating to operator preference only. The bronchial stump was covered 48 times on the right side (87%) and 9 times on the left side (20%)
Sfyridis *et al.* (2007) [11]	Randomized
Alifano *et al.* (2008) [12]	Not specified
Gudbjartsson (2008) [13]	Criteria unclear. The bronchial stump was covered intraoperatively in 73 patients (56%), of whom 25 (71.4%) were in the neoadjuvant group and 48 (50.5%) were in the first surgery group
Alan *et al.* (2009) [14]	Bronchial stump coverage was performed more frequently in those cases more likely to develop a BPF (right pneumonectomies, older patients, those who had previously taken immunosuppressive drugs); however, the final decision of whether to cover the bronchus was made by the operating surgeon
Kim *et al.* (2009) [15]	For right-sided resection, routine stump coverage with a pleural or pericardial fat pad buttress was performed
Mansour *et al.* (2009) [16]	The bronchial stump was routinely covered after right-sided pneumonectomy; the preferred technique was a pericardial fat pad placed below the superior vena cava
Panagopoulos *et al.* (2009) [17]	Coverage of the bronchial stump was routinely carried out in 91 cases of right pneumonectomy; regardless of the type of closure. On the left side, in 114 out of 130 mechanical closure pneumonectomies no further coverage of the bronchial stump was performed as protocol. Only in the remaining 16 cases where stump closure was manually performed, authors proceeded with additional coverage
Alloubi *et al.* (2010) [18]	Criteria unclear. Coverage of bronchial stumps had been performed with a pedicled well-vascularized flap in 55.0% of cases (intercostal flap, pericardial fat, azygos pleura)
Krasna *et al.* (2010) [19]	Bronchial stumps were generally covered with pedicled muscle flaps mobilized at the time of chest opening
Lidner *et al.* (2010) [20]	Criteria unclear. The choice of technique was determined independently of age, sex, tumor stage, side of surgery and perioperative chemotherapy or radiotherapy
Birdas *et al.* (2012) [21]	The study was based on patients with right pneumonectomy. Most patients who underwent bronchial closure also had soft tissue coverage of the bronchial stump in the form of pericardium, azygos vein, intercostal muscle or a combination



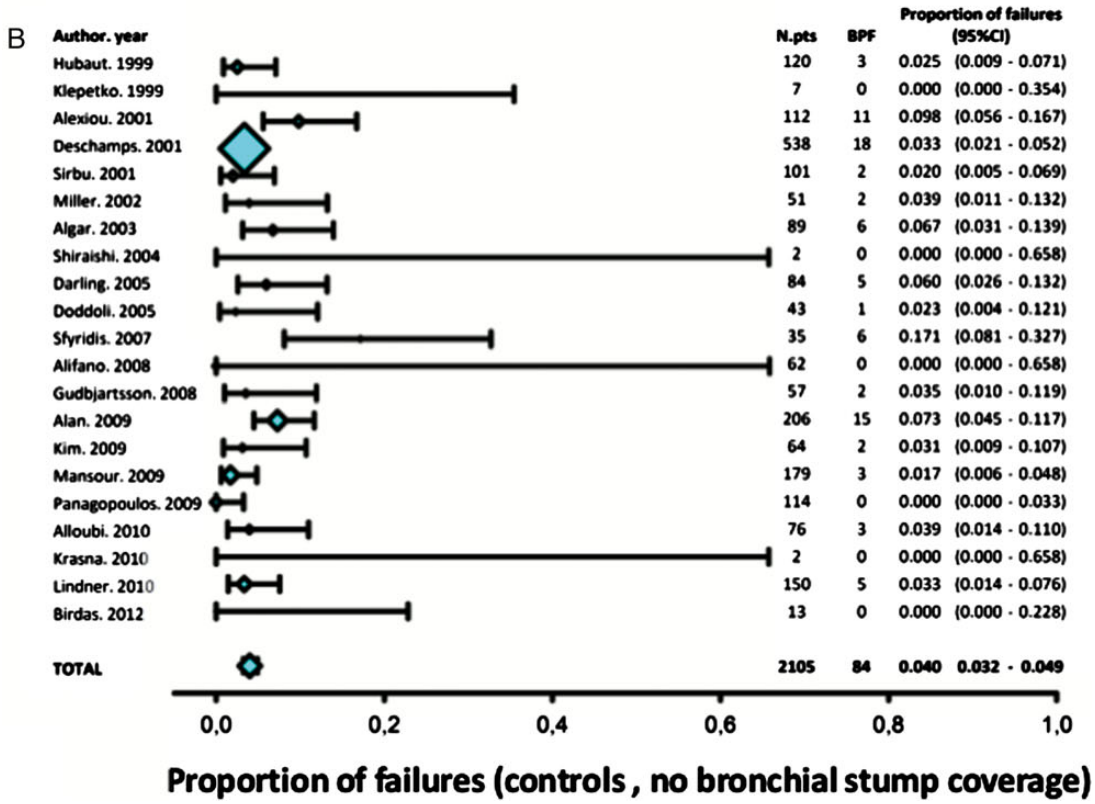


Figure 1: Forest plot of proportion of failures (bronchopleural fistula) in patients receiving bronchial stump coverage (**A**) and in patients not receiving bronchial stump coverage (**B**). For each single series and for the overall case series, the observed proportion and the 95% confidence interval (without continuity correction) were reported.

reported as conventional meta-analysis forest plots, with proportion of observed failures in each of the two patients' groups, and 95% CI. Diamond size is proportional to study numerosity.

Statistical analyses were performed using S-Plus (S-PLUS 6.0 Professional, release 1; Insightful Corporation, Seattle, WA, USA) and graphs using SigmaPlot 8.0 for Windows software package.

RESULTS

Overall, 21 series were eligible for the analysis, including a total of 3879 patients [1–21]. Of these, 1774 patients (45.7%) received BSC after pneumonectomy, while the remaining 2105 (54.3%) did not receive coverage. The number of patients included in each series was highly variable, ranging from 11 to 713 (median: 168).

Table 1 describes criteria reported in each publication for performing BSC or not. The decision to perform or not BSC was randomized only in one small trial [11]. In that trial, patients with diabetes mellitus undergoing pneumonectomy were randomized to have their bronchial stump reinforced with an intercostal muscle flap or to a conventional resection. Interestingly, the experimental group receiving an intercostal muscle flap had a lower incidence of BPF development, compared with the control group (0 vs 17.1%, respectively). In the 20 remaining publications [1–10, 12–21], the decision to perform or not BSC was not randomized: criteria were not explicitly specified in some cases, while, in the majority of publications reporting clear description of criteria used for the surgical technique, bronchial stump was routinely covered after right-sided pneumonectomy, considered at higher risk of BPF. Due to this bias in treatment decision, the baseline risk of failure (BPF) in the group of patients receiving BSC was systematically higher compared with the group of patients who did not receive coverage (Table 1).

In the series of patients receiving coverage, the proportion of BPF reported in each publication was variable, ranging from 0 to 33.3%. In the pooled population, the proportion of BPF was 6.3% (95% CI: 5.3–7.5%) (Fig. 1A).

In the series of patients not receiving coverage after pneumonectomy, the proportion of BPF reported in each study ranged from 0 to 17.0%. In the pooled population, the proportion of BPF was 4.0% (95% CI: 3.2–4.9%) (Fig. 1B).

DISCUSSION

We performed a systematic review of recently published series of patients undergoing pneumonectomy with or without BSC with any tissue, in order to quantify the risk of BPF in patients receiving or not receiving the coverage. In this series of papers, published between 1999 and 2012, the vast majority of patients considered at high risk for BPF received BSC. This common practice hinders an unbiased estimate of the efficacy of BSC in reducing the risk of fistula. The results of this meta-analysis show that, despite a clear negative selection, the incidence of BPF in patients considered at high risk and receiving coverage was only slightly higher compared with patients considered at low risk and not covered: 6.3 vs 4.0%.

Due to explicit selection bias, that is clear in the majority of the papers considered (as given in Table 1), the interpretation of the efficacy of BSC cannot be based on the direct comparison of proportion of failures in the group of patients receiving coverage compared with patients who did not receive it. This problem is clearly evident even considering the single reports in literature. In the largest series among those considered in our systematic review [4], all patients who underwent pneumonectomy at a single institution (the Mayo Clinic in Rochester, MN, USA), in a 13-year period (from 1985 to 1998) were reviewed for the occurrence of complications. At the univariate analysis, the bronchial stump reinforcement was associated with higher risk of BPF, but this "paradoxical" result is not surprising, because it was clearly driven by the higher baseline risk in the subgroup of patients receiving coverage. Despite that confounding result at the univariate analysis, and the absence of significant risk reduction at the multivariate analysis, the authors concluded that prophylactic reinforcement of the bronchial stump with viable tissue may be indicated in those patients suspected at higher risk for BPF. More than 10 years ago, Algar *et al.* [7] tried to clarify the real efficacy of bronchial coverage in preventing early BPF, and to determine independent risk factors for this complication after pneumonectomy. They reviewed 242 consecutive patients undergoing pneumonectomy for lung cancer, and 74% of the patients underwent BSC. At multivariate analysis, coverage of the bronchial stump was among the independent predictors of BPF: in detail, odds ratio of developing BPF was equal to 5.22 for patients not covered versus covered patients. Other independent risk factors were bronchial stump length, mechanical ventilation, previous chronic obstructive pulmonary disease, right pneumonectomy. However, although the results of this multivariate analysis are suggestive in favour of the efficacy of the procedure, in the absence of large randomized trials, the benefit associated with the coverage of the bronchial stump in preventing BPF remains controversial [7]. For instance, while the majority of groups perform the BSC for right pneumonectomies, because the left bronchial stump is considered to be more protected within the mediastinal structures, other authors advocate the need of similar coverage for left pneumonectomies, mainly in cases of patients considered at potential risk for BPF [1, 2].

We are aware that our results cannot produce high-level evidence, due to intrinsic limitations of available literature and because the two groups were explicitly not comparable in terms of baseline risk. That is the reason why we decided not to perform a formal statistical comparison between the two groups. However, our results probably reinforce the evidence of utility of BSC, because, although the baseline risk (according to known risk factors) in the group of patients receiving coverage was actually much higher, the failure rate in that group was only slightly higher than the group of patients that was not covered. Ideally, a randomized trial would help answer the question. Patients undergoing pneumonectomy could be randomized to BSC, and stratification for the commonly considered and accepted risk factors could be applied, in order to ensure internal validity and comparability between groups. However, part of the surgical community will probably consider the trial unfeasible, because many centres perform BSC in all cases considered at risk, although in the absence of randomized evidence supporting this strategy.

Conflict of interest: none declared.

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