Original Article

Impact of Intraoperative Blood Loss on Long-Term Survival after Lung Cancer Resection

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Purpose: The purpose of this study was to clarify relationships between intraoperative blood loss (IBL) and long-term postsurgical survival in lung cancer patients.
Methods: We retrospectively analyzed 1336 patients undergoing surgery: lobectomy in 1016, sublobar resection in 174, pneumonectomy in 106, and combined resection with adjacent organs in 40. The lobectomy group was stratified further by pathologic stages; overall survival difference was examined according to amount of IBL.
Results: Volume of IBL differed significantly according to surgical procedure when all patients were included. Within the lobectomy group, IBL differed significantly between gender, pathologic stage, histologic type (adenocarcinoma vs. non-adenocarcinoma), and year of operation (1983 to 2002 vs. 2003 to 2012). After stratification by pathologic stage, survival differed with IBL for stages IB to IIIB. Multivariate analysis identified gender, patients age (<69 vs. ≥69), pathologic stage (IA to IIB vs. IIIA to IV), year of operation, histologic type, and IBL as significant predictors of survival.
Conclusion: Since degree of IBL is an independent predictor of overall survival after lung cancer resection, IBL should be minimized carefully during surgery.

Keywords: intraoperative blood loss, lobectomy, lung cancer, prognosis, surgery

Introduction

Since volume of intraoperative blood loss (IBL) reflects degree of surgical invasiveness, IBL could affect patient outcome. However, associations between IBL and long-term postoperative survival in patients with lung cancer have been reported only rarely. Generally, IBL is likely to increase as tumors progress, since difficulty of complete tumor removal depends on extent of tumor invasion.

If a survival difference according to IBL existed in patients at the same pathologic stage who underwent resection by the same surgical method, a survival difference could have been caused by IBL or IBL-related events such as perioperative blood transfusion.

Perioperative blood transfusion frequently has been reported to worsen prognosis in patients with various malignant tumors[1–4] including lung cancer.[5,6] In some of these reports, immune suppression after blood transfusion was emphasized as the reason for a worse prognosis. However, conflicting results denying adverse effects of transfusion also have been reported.[7–11] In a systematic review[12] analyzing 5378 patients with lung cancer from a total of 19 articles, half of the papers mentioned significantly increased risk of recurrence associated with transfusion; the other half noted no adverse effects of transfusion. The authors of the review concluded that no consensus was evident from the presented evidence

about whether blood transfusions were associated with poorer outcomes after resection for lung cancer. Since blood products transfused have changed considerably over the past 30 years –from whole blood to packed red blood cells (PRBC) and leukocyte-depleted RBC– one would encounter difficulty in analyzing the effects of the various transfusions given over this long period.

Perhaps more informative than blood transfusion, greater volume of IBL has been reported to be a negative prognostic factor for patients with cancers of prostate,[13] pancreas,[14] colon and rectum,[15] and liver.[16,17] We therefore retrospectively analyzed the relationships between IBL and various clinicopathologic factors in lung cancer patients who underwent surgery in order to clarify whether extent of IBL affected long-term postoperative patient survival.

Patients and Methods

From January 1983 to December 2012, a total of 1336 patients underwent resection of lung cancer in our hospital. Operative records and pathologic reports in our database of lung cancer were reviewed to obtain the necessary information. Operative methods included lobectomy or bilobectomy in 1016, sublobar resection including segmentectomy and wedge resection in 174, pneumonectomy in 106, and combined resection with adjacent organs in 40. Standard dissection of lymph nodes (ND2a) was performed in lobectomy or larger resection. Sampling of lymph nodes was done in segmentectomy, and no lymphadenectomy was done in wedge resection. A final diagnosis of lung cancer was obtained from the resected lung specimen in all cases. Postoperative pathologic stages of patients were determined according to the most recent international staging criteria for lung cancer, published by the International Association for the Study of Lung Cancer in 2009.[18] The mean postoperative follow-up period was 37 ± 34 months (range, 1 to 219). This retrospective study was approved by the Institutional Review Board of our institution.

Statistical software used was StatView ver 5.0 (SAS Institute Inc., Cary, North Carolina, USA). Values were compared between 2 groups by the non-parametric Mann-Whitney U test, while values were compared among 3 groups or more by the Kruskal-Wallis test. Estimated overall survival rate after surgery was calculated by the Kaplan-Meier method, and survival differences between patient groups were tested by the log-rank test. In survival studies to confirm the effects of IBL, patients in

each group were divided into 2 subgroups of equal size according to amount of IBL (median or less vs. exceeding the median). A multivariate analysis was carried out according to the Cox regression model to identify independent risk factors. Values of p below 0.05 were considered significant for all statistical tests.

Results

Including all 1336 patients, IBL varied with operative choices closely linked to extent of lung cancer progression; greatest blood loss was observed in patients undergoing combined resection, followed in turn by patients undergoing pnemonectomy; lobectomy; and lastly, sublobar resection (p <0.0001, **Table 1**). After confirming that operative methods were associated significantly with IBL, further analyses were limited to the lobectomy group.

Profiles of 1016 patients undergoing lobectomy are shown in **Table 2**. In this group, a significant survival difference was obtained between subgroups defined by volume of IBL (p <0.0001). Additionally, IBL differed significantly by gender (p <0.0001), pathologic stage (p <0.0001), histologic type (adenocarcinoma vs. non-adenocarcinoma; p <0.0001), and year of operation (1983 to 2002 vs. 2003 to 2012; p <0.0001).

In each stratified disease stage within the lobectomy group, a significant survival difference related to IBL was found in pathologic (p-) stages IB (p = 0.0002), IIA (p = 0.0043), IIB (p = 0.0027), IIIA (p = 0.0002), and IIIB (p = 0.0483); differences in p values showed a lesser trend in p-stages IA (p = 0.0589) and IV (p = 0.0600, **Fig. 1A–1G**).

Univariate analysis by the log-rank test identified IBL, gender, patient age (<69 vs. ≥69), p-stage (IA to IIB vs. IIIA to IV), histologic type, and year of operation as significant predictors of survival (**Table 2**). Multivariate analysis identified all of these factors including IBL as significant predictors of survival (**Table 3**).

Discussion

This study found IBL in surgery for lung cancer to be associated closely with operative procedure, gender, disease stage, histologic type, and year of operation. Difference of IBL between both gender may be due to difference in average body size and difference in proportion of adenocarcinoma. Since non-adenocarcinomas including squamous cell carcinomas are more centrally located

Table 1   Intraoperative blood loss in surgery for lung cancer by procedure

Procedure	Patient number	IBL (mL, mean ± SD)	p value[a]
Lobectomy	1016	445 ± 449	
Sublobar resection	174	88 ± 166	
Pneumonectomy	106	908 ± 790	
Combined resection	40	1171 ± 810	<0.0001
Total	1336	457 ± 524	

[a]: Kruskal-Wallis test. IBL: intraoperative blood loss; SD: standard deviation

Table 2   Intraoperative blood loss and survival in 1016 patients who underwent lobectomy for lung cancer

	Patient number	IBL (mL, mean ± SD)	p value	5-year survival (%)	p value
IBL					
≤318 mL	509	176 ± 81		73.6	
>318 mL	507	713 ± 504	<0.0001[a]	45.0	<0.0001[b]
Gender					
Male	640	525 ± 510		49.8	
Female	376	307 ± 269	<0.0001[a]	73.9	<0.0001[b]
Age					
<69	553	431 ± 403		62.9	
≥69	463	460 ± 499	0.7622[a]	53.1	0.0082[b]
Pathologic stage					
IA	402	330 ± 322		81.7	
IB	220	415 ± 434		62.6	
IIA	92	499 ± 403		56.9	
IIB	71	644 ± 609		24.5	
IIIA	192	568 ± 517		31.8	
IIIB	10	722 ± 613		20.0	
IV	29	674 ± 680	<0.0001[c]	10.2	<0.0001[b]
IA–IIB	785	402 ± 408		67.7	
IIIA–IV	231	588 ± 543	<0.0001[a]	28.8	<0.0001[b]
Histologic type					
Ad	660	373 ± 354		63.6	
Non-Ad	356	577 ± 564	<0.0001[a]	48.9	<0.0001[b]
Year of operation					
1983–2002	555	588 ± 485		47.6	
2003–2012	461	272 ± 328	<0.0001[a]	72.4	<0.0001[b]
Total	1016	445 ± 449		58.3	

[a]: Mann-Whitney U test, [b]: Log-rank test, [c]: Kruskal-Wallis test. Ad: adenocarcinoma; IBL: intraoperative blood loss; Non-Ad: non-adenocarcinoma; SD: standard deviation

and locally invasive compared to adenocarcinomas, IBL is speculated to increase in non-adenocarcinomas. The large number of factors could confound attempts to evaluate effects of IBL on patient outcome. Since large IBL is likely in surgery for advanced lung cancer with a worse initial prognosis, high IBL might be indirectly associated with shorter survival. Therefore, in order to compare similar patients, we grouped patients undergoing lobectomy according to p-stage. Significant survival differences by IBL were obtained in p-stages IB, IIA, IIB, IIIA, and IIIB. In a multivariate analysis including known prognostic factors, IBL remained an independent predictor of survival in patients undergoing lobectomy. In survival analysis, postoperative death within 30 days after operation was found in 10 cases (0.98%) in the lobectomy group. Nine cases were postoperative infection or pneumonia including acute exacerbation of interstitial pneumonia. Death due to intraoperative massive bleeding was only one case in p-stage IV. Removal of these cases from the analysis did not change the survival results concerning IBL.

In our present study, we focused on IBL without considering perioperative blood transfusion, which had been identified as a factor worsening survival after resection
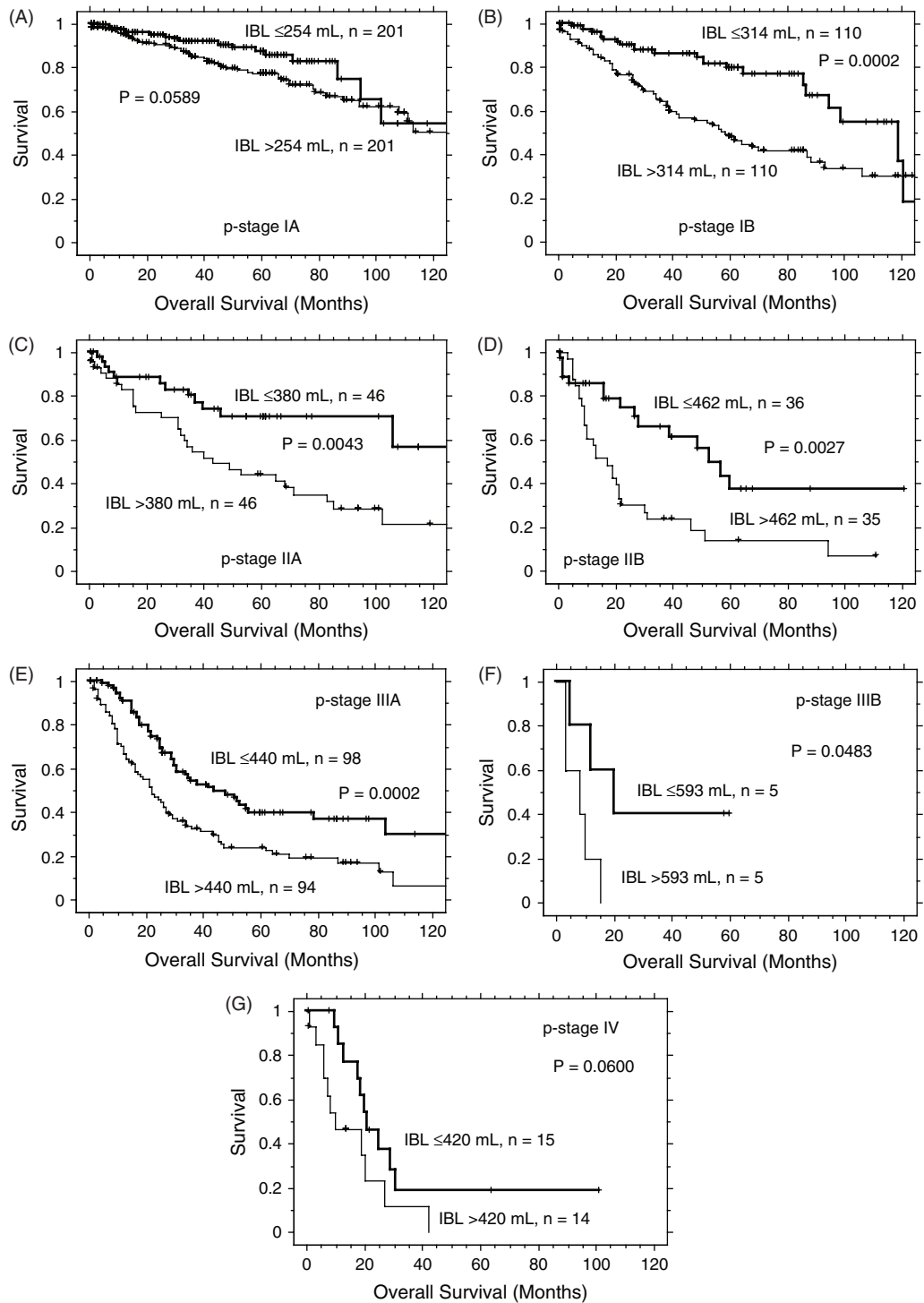
Fig. 1 Kaplan-Meier survival curves according to the amount of intraoperative blood loss (IBL) for patients undergoing lobectomy at various pathologic (p-) stages. (**A**) p-IA, (**B**) p-IB, (**C**) p-IIA, (**D**) p-IIB, (**E**) p-IIIA, (**F**) p-IIIB, and (**G**) p-IV. In each instance, the median amount of IBL was used as the cut off value between equal size groups. Significance was found in p-stage IB to IIIB but not in p-stages IA and IV.

Table 3 Multivariate analysis by the Cox regression model in patients undergoing lobectomy

Characteristics	p value[a]	Hazard ratio (95% CI)
IBL, ≤median	0.0004	0.647 (0.510–0.822)
Gender, female	<0.0001	0.551 (0.428–0.710)
Age <69	0.0035	0.735 (0.598–0.904)
p-stage, IA-IIB	<0.0001	0.360 (0.291–0.445)
Histologic type, Ad	0.0201	0.774 (0.623–0.961)
Year of operation, 2003–2012	<0.0001	0.528 (0.408–0.684)

[a]: Cox regression model. Ad: adenocarcinoma; CI: confidence interval; IBL: intraoperative blood loss

of lung cancer in several studies.[5,6] An initially postulated basis for worse prognosis involves immune modulation effects from passenger leukocytes present in allogeneic whole blood transfusions.[19] Recently however, even leukocyte-depleted blood transfusion was reported to be associated with decreased survival in lung cancer resection patients.[20] Another study fully disagreed, concluding that neither allogeneic nor autologous blood transfusion had an independent, adverse survival impact in lung cancer patients treated with radical resection.[11] Numbers of patients requiring perioperative blood transfusion in lung cancer surgery have decreased dramatically since IBL has been decreased by new, less invasive surgical procedures such as video-assisted thoracoscopic surgery. In this study we analyzed IBL rather than blood transfusion to avoid difficulties in interpreting data influenced by changing blood product preferences.

Though we cannot deny possible adverse effects of blood transfusion in this study, we hypothesized that massive IBL can directly promote spread of cancer cells into circulating blood and induce immune dysfunction by decreasing numbers of leukocytes available to engage in anti-tumor immunity. An experimental study using a rat model showed that blood loss, 1 day prior to tumor challenge had a profound stimulating effect on tumor growth, while natural killer (NK) cell activity of cells from the spleen was significantly depressed 24 h after blood loss.[21] Since NK cells are considered to participate in clearance of tumor cells from the circulation, enhanced tumor growth observed after blood loss might be caused by depressed NK function. Similarly, in a mouse model, NK cell cytotoxicity was significantly decreased 4 days after operative blood loss; the decrease correlated with the total amount of blood loss.[22] Clinical studies have suggested that blood loss and surgical injury suppress cell-mediated immune responses through depression of

macrophage antigen presentation capacity, depressed mitogenic response of T lymphocytes, and decreased T-helper 1 (Th1) lymphokines.[23] Recent clinical trials in patients with non-small cell lung cancer using antibody-mediated immune checkpoint molecule blockade[24,25] demonstrated importance of tumor immunity in controlling tumor growth. Therefore, a large IBL with or without blood transfusion likely would worsen the prognosis of patients undergoing resection of lung cancer.

Though statistically significant survival differences related to IBL were found in p-stages IB to IIIB, significance was not found in p-stages IA and IV. In p-stage IA, complete removal of cancer cells usually can be accomplished by surgery alone, so postoperative immune suppression from operative bleeding might not significantly affect relapse of lung cancer. In contrast, in p-stage IV, cancer cells already have spread through the circulation at the time of surgery, so immune suppression from bleeding may have limited effect on survival.

Only retrospective studies can provide data concerning association between IBL and postoperative survival, since prospective studies controlling for IBL are unethical. Since retrospective studies involve many confounding factors, multivariate analysis is essential for interpretation of study results. As IBL was selected as an independent predictor of survival among known prognostic factors, we believe that IBL can be an important determinant of patient outcome.

Conclusion

Our study identified degree of IBL as an independent predictor of overall survival after lung cancer resection. Since implications extend considerably beyond the perioperative period, we should take pains to minimize IBL in surgery for lung cancer in order to improve long-term outcome.

Disclosure Statement

No conflict of interest is declared.

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