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Edelweiss: Cancer

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Research Article

2689-6737

Frozen Section Assessment of Bronchial Margins during Lung Carcinoma Surgeries: Report of the Experience at a Single Institution

Siba El Hussein^{1*}, Roy Williams² and John Alexis³

Affiliation

¹Department of Hematopathology, MD Anderson Cancer Center, Houston, USA

²Department of Thoracic Surgery, Mount Sinai Medical center, New York, USA

³Department of Pathology, Mount Sinai Medical center, New York, USA

*Corresponding author: Siba El Hussein, Department of Hematopathology, MD Anderson Cancer Center, USA, E-mail:

elhusseinsiba@gmail.com

Citation: El Hussein S, Williams R and Alexis J. Frozen section assessment of bronchial margins during lung carcinoma surgeries: report of the experience at a single institution (2019) Edelweiss Cancer OA 1: 25-28

Received: Jul 06, 2019

Accepted: Jul 17, 2019

Published: Jul 24, 2019

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Abstract

Introduction

Many thoracic surgeons consider frozen section analysis of bronchial margins during lobectomies “obligatory” although routine frozen section analysis of the bronchial margin rarely yields positive results and infrequently changes intra-operative management in patients undergoing Non-Small Cell Lung Carcinoma (NSCLC) resection.

Materials and methods

234 cases of lobectomies with carcinoma were reviewed at our institution to assess bronchial margin involvement, correlation between frozen section and final bronchial margin status, gross distance between tumor and margin, and tumor type.

Results

Tumor distance to margin varied in the 234 cases from grossly involved to 10 cm away. 5 cases out of 234 (approximately 2.1%) had a positive bronchial margin in the final report. 3 out of the 5 cases were poorly differentiated squamous cell carcinoma grossly abutting the bronchial margin, two cases were of poorly differentiated adenocarcinoma located grossly 0.5 cm away from the bronchial margin. 4 out of 5 cases were called positive intra-operatively. In none of the 4 out of the 5 positive cases did frozen section exam of the bronchial margins change the intra-operative management of the case.

Conclusion

Our study supports selective use of intra-operative frozen section of bronchial margins during lobectomies for carcinoma. On the basis of our findings, a distance of approximately 1 cm or less is suggested as a threshold for intra-operative microscopic examination of the bronchial margins. However, routine examination of the bronchial margins, regardless of the location of the tumor upon gross examination, and in the absence of empirical evidence supporting this practice, is only time consuming intra-operatively, wasteful of resources and has no therapeutic or prognostic value.

Keywords: Lung carcinoma, Bronchial margin, Tumor, Adenocarcinoma, Adenoid cystic, Carcinoma in Situ.

Abbreviations: NSCLC-Non-small Cell Lung Carcinoma, IASLC-International Association for the Study of Lung Cancer, AJCC-American Joint Committee on Cancer, CIS-Carcinoma in Situ.

Introduction

Many thoracic surgeons consider frozen section analysis of bronchial margins during lobectomies “obligatory” to ensure complete local resection of the tumor in patients undergoing Non-Small Cell Lung Carcinoma (NSCLC) resection. However, “routine” frozen section analysis of the bronchial margin, without taking into consideration the anatomic relationship of the tumor to the bronchial margins, rarely yields positive results and infrequently changes intra-operative management. In addition, the impact of residual microscopic disease on patients’ prognosis is a controversial topic

That has been discussed extensively in literature with contradictory results in which some authors claim adverse outcomes in patients with residual disease, while others have demonstrated that residual disease per se is not necessarily linked to poor prognosis post lobectomy.

Materials and Methods

Pathology reports of 234 cases of lobectomies with carcinoma (squamous cell carcinoma, adenocarcinoma, and neuroendocrine carcinoma) performed between March 2013 and March 2016 at Mount Sinai Medical Center were reviewed to assess: Bronchial

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margin involvement by carcinoma, correlation between frozen section and final bronchial margin status, gross distance between tumor and margin, and tumor type. In addition, operative reports of cases positive for bronchial margin involvement by carcinoma at time of frozen section were reviewed to look for change in surgical management following intra-operative consultation.

Results

Tumor distance to margin varied in the 234 cases from grossly involved to 10 cm away. 5 cases out of 234 (approximately 2.1%) had a positive bronchial margin in the final report. 3 out of the 5 cases were poorly differentiated squamous cell carcinoma grossly abutting the bronchial margin, and two cases were of poorly differentiated adenocarcinoma located grossly 0.5 cm away from the bronchial margin. 4 out of 5 cases (2 squamous cell carcinoma cases, and 2 adenocarcinoma cases) were called positive intra-operatively. However, in none of the 4 out of the 5 positive cases did frozen section exam of the bronchial margins change the intra-operative management. In 1 case out of 5, the tumor was located 0.5 cm away from the bronchial margin. The bronchial margin was not examined at frozen section in this particular case, however permanent sections revealed margin involvement by poorly differentiated adenocarcinoma and adenocarcinoma in-situ.

Discussion

Applications of frozen section analysis of the bronchial margins

Despite the common misconception in surgery and pathology, that frozen section assessment is “obligatory”, the National Comprehensive Cancer Network for treatment of NSCLC doesn't include “routine” frozen section assessment of the bronchial margins in its guidelines [1].

Frozen sections are essentially helpful in the setting of central tumors, since these tumors tend to have a microscopic extent beyond the grossly visible limits. On the other hand, peripheral tumors less frequently extend into the bronchial margins. This can be partially explained by the fact that squamous cell carcinomas (centrally located in the majority of times) tend to show bronchial extension slightly more frequently than adenocarcinomas (peripherally located in the majority of times). In addition, squamous cell carcinomas are typically mucosal whereas adenocarcinomas' spread tends to be peri-bronchial [2].

Positive margin detection by frozen section rarely leads to intra-operative change in surgical management of the patient due to decreased patient's tolerance to: (I) increased length of operation and (II) resection of lung tissue. In addition, the discovery of advanced lung disease, intra-operatively, may render further intervention of no clinical benefit to the patient [3].

False positive and false negative interpretations

False positive margins have been reported by pathologists in certain scenarios where benign structures acquire morphological alterations (metaplasia, radiation changes, and crushing artifacts) leading to confusion with a malignant process. Examples are squamous metaplasia interpreted as carcinoma in-situ, radiation changes interpreted as suspicious for malignancy and lymphocytic infiltrates interpreted as small cell carcinoma [2].

False negative margins can be due to sampling errors, when the margins are not embedded on the correct side during intra-operative evaluation. This may lead to an initial negative margin at time of frozen section; however the carcinoma may appear in the permanent

section. Another scenario that might lead to false negative margins is diagnostic error, where pathologists either misinterpret malignant cells as benign cells, or miss the subtle malignant cells in the field, partially due to the inherent suboptimal architecture and structural details frozen section analysis provides [2].

Request for frozen section analysis of bronchial margins tailored to patients' unique presentation

In 2012, Owen et al. have recommended the selective use of frozen section assessment of bronchial margins only when positive results would lead to changes in the surgical management intra-operatively. In addition, they recommended abstinence from frozen sections when: [I] the surgeons know that the patient won't tolerate extra procedures, [II] in locally advanced disease noted intra-operatively, [III] and in small, peripherally located carcinomas. Implementing these recommendations can decrease the length of operations by 10%, which in turn decreases the utilization cost of the operating room and the exposure of patients to extra anesthesia, and cuts unnecessary spending by health care providers. Once thoracic surgeons decide to change the surgical management following an intra-operative positive bronchial margin, examples of additional surgical interventions include: Bronchoplasty, sleeve lobectomy, bilobectomy or pneumonectomy [3].

The role of gross examination of the bronchial margins

Gross examination of the bronchial margins is justified in cases of peripherally located carcinomas as these tend to be confined peripherally and rarely show microscopic extension to the bronchial margins. “Safe margins” suggested in literature range from 1.5 to 3 cm. Our study suggests a distance of approximately 1 cm or less as a threshold for intra-operative microscopic examination of the bronchial margins [2, 4-7].

Frozen section assessment is essential in certain scenarios to ensure that margins have been adequately evaluated, as bronchial involvement by carcinoma can be missed during gross examination in several cases. Examples of these scenarios include: involvement of the mucosa by carcinoma in-situ (typically in cases of squamous cell carcinomas), microscopic extension of the tumor into the peri-bronchial tissue notably in cases of adenocarcinomas, salivary gland carcinomas (adenoid cystic and muco-epidermoid types) and neuroendocrine tumors and peri-bronchial lymph node or lymphatic channel invasion [2].

“R” for residual disease

The letter “R” (for residual) is added by the 7th edition of the International Association for the Study of Lung Cancer (IASLC)/American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) TNM (tumor, node, metastasis) classification to describe the presence or absence of residual tumor after treatment. The bronchial margin status is classified as R0 when it is grossly and microscopically uninvolved by carcinoma, R1 when grossly uninvolved but microscopically positive for carcinoma and R2 when it is grossly involved by carcinoma [8].

A tool with high sensitivity to detect mucosal involvement of the bronchial margin by CIS is auto-fluorescence endoscopy, however this method does not detect extra-mucosal involvement (e.g: peri-bronchial invasion) by carcinoma, in addition the application of this test is limited by its high cost [9].

In a study conducted by Massard et al. half of the patients with residual carcinoma in-situ had multiple primary squamous cell carcinomas. In addition, 12 out of their 32 patients with squamous cell lung carcinoma had a previous history of bronchial or head and



neck squamous cell carcinoma, or developed a second primary squamous cell carcinoma during follow-up. Massard et al. brings up an interesting point that patients with multiple primary squamous cell carcinomas may have an underlying “field effect” characterized by areas of mucosal atypia, with coexisting areas of carcinoma in-situ that may transform with time into carcinomas. This is of importance because such patients should be considered high risk for potentially developing residual disease (arising from an in-situ process) or a new primary, post-surgery, of lung squamous cell carcinoma [10].

Carcinoma In Situ (CIS) at the bronchial margins does not affect survival rate

In 1959, Cotton classified residual disease into mucosal and extra-mucosal, and suggested that different types may have different prognoses [6]. In 1974, Martini et al. suggested that the presence of Carcinoma In-Situ (CIS) at the bronchial margin does not seem to affect survival and was not a sufficient reason for an extensive surgery [11].

In 1979, Soorae and Stevenson further sub-classified R1 disease into “mucosal tumor” including carcinoma in-situ and invasive carcinoma, and “extra-mucosal” tumor including direct peri-bronchial and lymph node invasion by tumor or submucosal lymphangitic spread. In their study they showed that isolated CIS did not affect survival, contrary to the other 3 subtypes (direct mucosal involvement by invasive carcinoma, involvement of peri-bronchial tissue and lymphatic permeation), with 5-year survival rates of 70%, 21%, 17% and 0%, respectively [11,12].

In 1982, Law et al. following their study that showed a 5-year survival rate of 75% for patients with CIS in the bronchial margin came up with the same conclusion that involvement of the bronchial margin by CIS does not affect survival rate [13]. In 1994, Tan et al. noted that the survival rate of patients with CIS at the bronchial margin was not different from patients with microscopically uninvolved bronchial margin [14].

In 1998, Snijder et al. after conducting a study of patients with stage (I) Non-Small Cell Lung Cancer (NSCLC), reported that the 5-year survival rate of patients with R1(CIS) group was 58%, close to the survival rate of the R0 group (54%), and remarkably better than the survival rate of the R1 (non-CIS) group (27%) [15]. In 2005, Aubert et al. concluded in their published abstract that the presence of CIS at or near the bronchial margin did not affect the long term survival [16].

In 2008, Kawaguchi et al. noted in their study that the 5-year survival rate of patients with R1 (CIS) was 63% compared to other R1 groups (R1 with direct mucosal extension by invasive cancer had a 5-year survival rate of 0%, and R1 with lymphatic permeation and peri-bronchial infiltration had a 5-year survival rate of 10%). In 2009, Callaud et al. described 3 cases of R1 (CIS) N0 NSCLC with a survival rate beyond 5 years without additional treatment [17, 18].

Poor performance of R1 groups might be correlated with an advanced underlying disease

In 2000, Massard et al. concluded in their study that R1 (CIS) does not influence survival per se and that the poor prognosis attributed to R1 with peribronchial infiltration was correlated with an underlying advanced disease stage and was almost always associated with positive N (lymph node) status [10].

In 2009, Fernandez et al. reported 52 patients with R1 (CIS) who survived beyond 30 days post-surgery among 80 patients with bronchial margin involvement by carcinoma. However the median survival of the 52 patients with R1 (CIS) was only 25 months, and

this can be well explained by the fact that 29 of the 52 patients had advanced stages (III or IV) at the time of surgery [19].

Management of positive residual disease at the bronchial margin

The prevalence of positive margins in our study was 2.1%, which falls at the lower end of the range reported by other studies (1.5 to 14.7%) [2, 12, 20]. There are different ways to manage R1 (microscopic residual disease) patients. To tackle this task, Massard et al. suggested sub-classifying R1 groups into an intra-mucosal disease group and a peri-bronchial residual disease group. The intra-mucosal disease groups is thought to have higher chances of spontaneous regression with time, and are managed with either a “wait and see” policy or an active surveillance policy that includes repeated endoscopy and CT scan at 3 months intervals. If a positive margin is detected on biopsies during scheduled endoscopies, photodynamic therapy is offered. The second group consisting of R1 patients with peri-bronchial residual disease can be managed with re-operation for complete clearance at the surgical site, or may be treated with radiotherapy, which have shown to be efficient in controlling local recurrences, but with high risk adverse effect on the long term survival [10].

Conclusion

Detection of a positive bronchial margin by frozen section rarely leads to intra-operative change in surgical management of the patients. Frozen sections are essentially helpful in the setting of central tumors, since these tumors tend to extend microscopically beyond the grossly visible limits. However, gross examination of the bronchial margins is justified in cases of peripherally located carcinomas. Selective use of frozen section assessment of bronchial margins is recommended when positive results would lead to changes in the surgical management intra-operatively.

Abstinence from frozen sections is recommended in locally advanced disease, in small peripherally located carcinomas and in patients known to be poor candidates for extensive operation. Pathologists should be aware of sampling errors during frozen sections, leading to false negative results, and of the existence of particular scenarios (e.g: metaplastic and radiation changes and crushing artifact), that can lead to false positive results.

Review of literature demonstrates that Carcinoma in Situ (CIS) at the bronchial margins does not affect survival rate, and that poor performance of patients in this group (R1 group) is likely due to an underlying advanced disease stage. Management of patients with microscopic residual disease differs between groups with intra-mucosal involvement and peri-bronchial involvement. Suggested management options include a “wait and see” policy, an active surveillance with periodic endoscopy and CT scan, re-operation to clean the surgical site from residual disease and radiotherapy.

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