Carcinoma In Situ at the Bronchial Resection Margin

A Review

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Abstract: Carcinoma in situ at the mucosal bronchial resection margin is a rarely reported event. At present, such histological findings at the resection margins are classified as R1(is), thus representing an incomplete resection. A review of the English literature on the topic was undertaken to try to better define the significance of such findings and to define possible areas of prospective data acquisition to further define the problem and its management.

Key Words: Carcinoma in situ, Bronchial resection margin, NSCLC.

The presence of carcinoma in situ (CIS) at the mucosal bronchial resection margin has been reported in 0.05 to 2.5% of surgical series.[1–13] As per 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) tumor, node, metastasis (TNM) classification, the letter R may be used as an additional descriptor to the TNM descriptors to define the absence or presence of residual tumor at the primary tumor site after its treatment. After lung cancer resection, the bron-

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chial margin status can thus be classified as R0 when the margin is clean of all malignancy both grossly and microscopically, R1 when the margin is grossly uninvolved but microscopically positive and R2 in the presence of grossly positive margins. Presently, the presence of CIS at the bronchial margin is considered to represent R1 resected disease with the added qualifier (is) for in situ. However, it seems that the prognosis of R1(is) at the bronchial margin is much better than that of other R1 situations.[7,9,11] For that reason, a proposal by our committee published in 2005 suggested that the presence of CIS at the bronchial margin be considered an "uncertain resection," meaning a resection where there is no evidence of residual invasive tumor but one that does not fulfill all the criteria required to be designated as a complete resection.[14] A commentary published in Lung Cancer in 2004 by Kutlu et al.[15] even suggested that CIS at the margin should be considered R0. This controversy surfaced at one of the meetings of the International Staging Committee of the International Association for the Study of Lung Cancer (IASLC) where the management of such findings by the members of the Committee was anything but uniform.[14] At one end of the table, one group accepted such margin without further resection or additional treatment but recommended close endoscopic follow-up. Others favored surgical revision of the margin, at times converting a lobectomy to a sleeve lobectomy or even to a pneumonectomy. Some favored no further resection but recommended adjuvant radiotherapy to the stump area as one would consider after a true incomplete resection. Finally, the potential roles for postresection photodynamic or LIFE-guided laser therapies to the area were mentioned, if available.

In an effort to possibly establish management guidelines for such findings, a review of the available international literature was undertaken. A secondary objective for this review is to define potential areas of prospective data set acquisition that could help us in the future to further define the problem and its management.

MATERIALS AND METHODS

Surgical Series

CIS at the bronchial resection margin is only described in a very small percentage of the published series addressing the topic of residual disease at resection margins. A review of the English literature of the last 35 years contains 13 articles

TABLE 1. List of Surgical Series Addressing the Topic of Residual Disease at Resection Margins (1974–2010)

Reference	Period Covered	Population Studied	CIS (n)	Squamous Histology (n)	CIS % of Population Studied (%)	Local Recurrence (n)	Survival 5 yr (%); All	Survival 5 yr (%); N0
Martini et al.[1]	1947–1972	26	2	2		0	NA	
Soorae and Stevenson[2]	1968–1972	434	10	10	2.3	NA	70	
Law et al.[3]	1966–1975	1000	9	9	0.9	NA	66.7	75
Heikkila et al.[4]	1961–1970	1069	5	NA	0.5	NA	NA	
Whyte et al.[5]	1980–1986	560	2	2	0.4	NA	NA	
Tan et al.[6]	1986–1991	255	6	NA	2.4	NA	NA	
Snijder et al.[7]	1977–1993	834	12	9	1.4	5	58	58
Lacasse et al.[8]	1987–1990	399	3	NA	0.8	NA	NA	
Massard et al.[9]	1986–1997	>2000	20	20	1.0	NA	38.7	51.30
Ruffini et al.[10]	1993–2002	1090	5	5	0.5	NA	NA	
Kawaguchi et al.[11]	1976–2003	4493	9	9	0.2	1	63	
Collaud et al.[12]	1992–2000	584	3	3	0.5	2	100	100
Fernanez et al.[13]	1993–1997	2994	52	45	1.7	NA	NA	
Total		15,738	138	114	0.9			

CIS, carcinoma in situ.

that included and/or described a number of cases with CIS at the bronchial margin.[1–13] These series analyzed populations ranging from 255 to 4493 resected patients, and incidences of CIS at the margin varied from 0.02 to 2.4%. Cumulatively, out of approximately 16,000 resections reported in these series, 138 cases (0.9%) of CIS at the bronchial margin have thus been reported (Table 1).

Martini et al.[1] in 1974 published a report on 26 cases of radiologically occult lung cancers diagnosed and treated at Memorial Sloan-Kettering Cancer Center. In the 13 resected cases, CIS was found at the bronchial margin in two. Both patients received adjuvant radiotherapy. At 2 years, one remained free of disease. The other patient died at 6 years from a second lung cancer that developed at another site 5 years after initial surgery. The patient had no evidence of recurrence at the initial margin. In their discussion, the author suggested that CIS at the bronchial resection margin did not seem to affect survival and was not a sufficient reason to call for more extensive surgery.

In 1979, Soorae and Stevenson[2] from Belfast reported on 64 patients with positive margins after 434 consecutive lung cancer resections in a 5-year period. Ten of these had CIS at the margin (incidence 2.3%), all 10 of squamous cell histology, and seven survived 5 years or more after resection without further therapy (70%, 5-year survival). They concluded that isolated CIS at the margin did not affect survival contrary to the other three patterns of microscopic bronchial margin involvement described: direct mucosal extension by invasive cancer, lymphatic permeation, and involvement of peribronchial tissues with respective 5-year survival rates of 21%, 0%, and 17%.

In 1982, Law et al.[3] from the Royal Brompton Hospital in London described another nine patients with CIS at their margin from a retrospective series of 1000 consecutive patients who underwent lobectomy or pneumonectomy for lung cancer in a 10-year period (incidence 0.9%). All nine had squamous histology, and of the eight without mediastinal

nodal involvement, six survived 5 years (75%, 5-year survival). Similarly, it was concluded that CIS at the margin did not affect survival.

Heikkila et al.[4] in 1986 mentioned five cases of bronchial margin CIS included in a series of 44 cases of microscopic positive margins out of 1069 lung cancer resections performed at the University of Helsinki between 1961 and 1970. No additional detail was available.

A review from Liverpool published in 1988 reported two cases of CIS at the resected margin out of a resected population of 560 (incidence 0.35%). Both were of squamous histology and were alive free of disease 28 and 30 months after resection.[5]

At the British Thoracic Society meeting in December 1994, Tan et al.[6] from Aberdeen noted six cases of CIS at the margin out of 255 patients who had lung cancer resection between 1986 and 1991 (incidence 2.4%). The survival of these individuals was not different from the survival of patients with entirely benign histology at their bronchial margin.

Four years later, Snijder et al.[7] from the Netherlands reported on a series of 834 resected stages I non-small cell lung cancer (NSCLC). Twelve had CIS at the bronchial margin (incidence 1.43%). Three of these were adenocarcinoma, the balance were of squamous cell histology. Local recurrences were noted in five of the 12 CIS patients, and 75% of CIS patients experienced a recurrence of some sort, significantly more than in the true R0 group. Survival of this R1(is) group at 5 years was however 58%, similar to the survival of the R0 group at 54% and more than double the survival of the other R1 subgroup (i.e., non-CIS) at 27%. Having restricted their report solely to patients with N0 disease, this analysis truly eliminated the confounding N status in their evaluation of how marginal CIS may affect survival.

The same year, Lacasse et al.[8] of the Canadian Lung Oncology Group identified three patients with CIS at the

margin out of a group of 20 patients with incomplete R1 resections out of 399 patients who had participated in a multicenter randomized staging trial (incidence 0.75%).

The largest experience from a single institution reported to date is that of Massard et al.[9] from Strasbourg. Twenty cases of CIS at the margin were identified in a database of approximately 2000 resections performed over a period of 11 years. These made up one-half of a population of R1 resections which all together accounted for less than 2% of all resections performed during that period. All 20 CIS cases were squamous cell carcinomas: 13 were of N0 status, 6 were N1, and only 1 was N2. Ten of the 20 patients had more than one primary cancer before or after their recorded resection. Survival at 5 years was 38.7% for the 20 but rose to 51.3% for the N0 subset. Adjuvant radiation therapy was given in 17 of 20 patients, and the authors suggest that this may have been deleterious in this group of patients. As all previous authors have concluded, they observed that CIS at the margin did not influence survival per se. At the time this series was reported, in Strasbourg, the management of patients with CIS at the margin was for close follow-up with serial CT and bronchoscopy. Photodynamic therapy was being evaluated in the patients where early invasive cancer was identified during such follow-up.

In 2004, a group from Torino described their experience with associated preinvasive lesions in 1090 patients resected for lung cancer in a 10-year period. CIS at the resected margin was only seen in five patients, all of squamous histology. Two were treated with adjuvant radiotherapy. At the time of their report, two were alive free of disease 2 and 5 years after surgery and three had died of systemic metastases at 1, 2, and 3 years. Local recurrence rates were not mentioned in this small group of patients.[10]

In analyzing 74 patients with microscopic residual tumor at their bronchial margin out of 4493 patients who had undergone lung cancer resection at the National Cancer Center Hospital in Tokyo, Kawaguchi et al.[11] noted 9 with R1(is), all with squamous cell carcinoma histology, whose 5-year survival was 63%. Other R1 groups divided along the patterns described by Soorae and Stevenson[2] as patients with direct mucosal extension by invasive cancer ($n = 11$) or lymphatic permeation and involvement of peribronchial tissues ($n = 54$) had 5-year survival rates of 0% and 10%, respectively. Only one of the nine patients developed local recurrence (11%) and he was one of the five who had been given adjuvant radiation therapy. Contrary to the other patients with R1 disease in their series, the presence of CIS at the margin did not increase the risk of developing a postoperative bronchopleural fistula.

Two more series were reported in 2009. The first by Collaud et al.[12] from Geneva described three cases of CIS at the resection margin in a series of 35 patients with R1 resections out of the 584 consecutive interventions in 8 years. All three had N0 NSCLC and survived beyond 5 years without additional treatment. The other retrospective study reported in 2009 was from the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Thoracic Surgery (GCCB-S). From 1993 to 1997, 2994 patients underwent

thoracotomy in the management of their NSCLC by the members of the GCCB-S, and 80 had bronchial stump involvement, 72 surviving beyond 30 days after surgery. Of these, 52 had CIS at their margins and their reported median survival was only 25 months, likely a reflection of the fact that 29 of these had stages III or IV at surgery. Unfortunately, the data reported in the manuscript does not allow an in-depth analysis of these 52 cases.[13]

Finally, in a related but different review presented in Barcelona at the IASLC 11th World Lung Cancer Conference in 2005, Aubert et al.[16] presented a retrospective study of 1501 patients resected for stages I to IIIA NSCLC. CIS at or in the vicinity of the bronchial margin had been identified in 126 cases, and the authors concluded that the presence of CIS at or near the margin had no negative affect on long-term survival. The published abstract does not contain enough information, however, to further evaluate their findings.

It is of interest only to note that, in a recent article published in 2009, Riquet et al.[17] excluded R1(is) cases when studying the impact of R1 bronchial margins in a series of 4026 patients who had had R0-R1 resections from 1984 to 2006.

RESULTS

Thus, it seems that the presence of CIS at the resected bronchial margin is a rare reported event, especially in lung cancer cases with histology other than squamous cell carcinoma. From the reports where survival was analyzed specifically for patients with CIS at their bronchial margin, it seems that the presence of R1(is) does not negatively impact on the survival of our patients contrary to other R1 situations such as patients with direct mucosal extension by invasive cancer or lymphatic permeation and involvement of peribronchial tissues where survival is generally poor.[2,7,11]

The data reviewed unfortunately does not allow clearly separating the margin status from other prognostic factors such N status. Two reports confined their analysis to patients with N0 disease[7,12] for a total of 15 patients. Another series describes an overall 5-year survival of 38.7% for the 20 patients reported and a survival of 51.3% when restricting their analysis to patients with N0 disease, without specifically mentioning the 5-year survival rates of patients with N1 or N2 disease. In addition, the report from Finland compared the survival of all patients with R1 bronchial margins (including five cases with R1(is)) to those with R0 margins. In both groups, the survival of patients with stage I carcinoma was reported as significantly better than stage III. Also, the survival rates were identical in the two groups when evaluated by TNM.[4] Indirect evidence thus suggests that the survival is driven by the presence or absence of regional nodal involvement in these patients and not by the presence or absence of CIS at their margin.

It is apparent from this review that the actual literature addresses solely the behavior and prognosis of squamous CIS at the bronchial margins and that there is no information available at this time on the presence of the new proposed concept of adenocarcinoma in situ at resection margins.[18] In addition, there are insufficient data to conclude on the behav-

ior of CIS at the circumferential margins of resected peripheral adenocarcinomas. Of the 124 literature cases where the histology of the primary tumor is reported, 114 were of squamous histology (92%) (Table 1).

Finally, there are almost no data in these articles describing whether the CIS at the bronchial margin was associated with a peripherally located cancer or whether it was in proximity to an adjacent or nearby centrally located tumor. As such, it is impossible to address the hypothesis that maybe these two different scenarios should be considered and coded differently. For example, a centrally located squamous cell cancer with adjacent CIS at the bronchial margin could be coded R1(is). A peripheral tumor of any histology resected by lobectomy where the bronchial resection margin expresses CIS possibly could be coded as two different tumors: the peripheral lesion being R0 and the second Tis R1(is).

DISCUSSION

Skewed Population?

The series listed earlier only address the follow-up, recurrence patterns, and survival of individuals who were found to have CIS at the bronchial margin identified on final pathological analysis of the resected specimen. As such, it is unfortunately impossible from this review to comment on the behavior of individuals who may have initially had CIS identified by frozen section evaluation during surgery and in whom the surgeon elected to take the resection to a higher level in the bronchial tree to obtain a true R0 bronchial resection.

A Paradox?

In 1956, Habein et al.[19] in discussing cancer recurrence in the bronchial stump suggested that after pneumonectomy "the finding of metaplastic epithelium near the carina is of nearly as much prognostic significance as is the presence of frank carcinoma in this region." In 1959, Cotton[20] noted that 30% of the cases he reviewed after resection harbored "epithelial metaplasia" in the vicinity of the bronchial margins and thought it would be wise "to remove the tumors as widely as possible to avoid leaving behind potentially dangerous areas of epithelial change." The influential work of Auerbach et al.[21] demonstrated that preinvasive lesions (including CIS) were frequent in the bronchial epithelium of smokers and of patients with lung cancer. As a result of this study and others that followed, the concepts of field carcinogenesis and of the gradual and stepwise progression of early epithelial changes to metaplasia, mild, moderate, severe dysplasia toward CIS, and micro invasive bronchial cancers have developed.[22–23]

More recent reports on the follow-up of CIS identified by autofluorescence bronchoscopy in populations considered at high risk of developing lung cancer suggested that the majority of these lesions will indeed progress to invasive cancer on relatively short follow-up with some reporting 20% of progressions occurring in the first year and 66% within 36 months.[24–26] This observation certainly does not correspond to the postoperative observations described earlier. Are we dealing with the same disease? Is the pathology described as CIS in these reported retrospective surgical series really CIS

as a panel of experts would define it today?[25] Is there a possibility that CIS at the bronchial resection margins regresses spontaneously after removal of the nearby cancer as some have suggested: either from spontaneous regression after smoking cessation or by rendering the area relatively ischemic thus promoting regression, as a result of a local scarring phenomenon or through unknown local immunologic pathways?[2,3,23] Spontaneous regression of preneoplastic changes has been reported in 52% of lesions seen in nonsurgical high-risk individuals who had been found to harbor such changes on autofluorescence bronchoscopy in a recent report by Breuer et al.[27] from Amsterdam. An excellent review by Banerjee[22] in the *Journal of Thoracic Oncology* also recently emphasized that there is a discrepancy between the prevalence of preinvasive bronchial lesions and that of lung cancer, suggesting that not all lesions will develop into invasive cancer.

Adjuvant Radiotherapy Issues

There is very little and conflicting reports documenting the role of adjuvant radiotherapy in the management of residual CIS at the bronchial resection margin. Heikkila et al.[4] believed that adjuvant radiation therapy accounted for an improved survival after incomplete R1 resections. Massard et al.[9] also reported a low rate of local recurrence with the use of postoperative radiation therapy in marginal CIS, 15%, in contrast to more than 50% in a series by Snijder et al.[7]: most patients in the Massard series received adjuvant radiotherapy, but their data also suggested a deleterious effect on long-term survival. This is similar to what was seen in the PORT meta-analysis and we may suspect that the weaknesses of the radiation technique used were similar to those used in the PORT randomized trials.[28] Others have described the use of PORT after sleeve resections when CIS was seen at one of the bronchial margins.[29] Nevertheless, at this time, there is insufficient data to draw any conclusion on the role of adjuvant external beam radiation therapy in this situation. Considering this and taking into account the favorable survival and the low local recurrence rates reported, close follow-up might be the best alternative with a dedicated treatment in case of relapse. One series, however, has suggested very little role for surveillance white light bronchoscopy in these individuals owing to its low returns and the limited impact this procedure had in their hands in modifying patient management positively.[5]

Alternative experimental approaches mentioned, without published results to date, have included endobronchial brachytherapy or other novel endoluminal therapeutic modalities such as laser therapy with or without photodynamic therapy.[9,30]

Pathology Issues

By current standards squamous dysplasia in the bronchial mucosa is not regarded as a positive margin but CIS is. The debate being considered in this article is whether CIS should be regarded as a negative margin (R0) or microscopically positive margin (R1(is)).

R1 positive margins can be divided into (1) inner bronchial wall which can take the form of mucosal CIS or invasion of submucosal tissues; (2) outer bronchial wall and

TABLE 2. Classification of Positive Margin of Resected Bronchus

Inner bronchial wall
Mucosal CIS
Submucosal tissues
Outer bronchial wall and peribronchial or perivascular tissues
Direct extension of primary tumor
Invasion from nearby lymph nodes with metastases
Lymphatic permeation: submucosal or peribronchial lymphatics
Detached luminal floating tumor fragments from papillary or polypoid
tumor without attachment to the bronchial wall

CIS, carcinoma in situ.
Modified from *J Thorac Cardiovasc Surg* 1979;78:175–180 and *Thorax* 1982;37:492–495.

peribronchial which can take the form of direct extension of the primary tumor or invasion from nearby metastatic tumor into lymph nodes; (3) lymphatic invasion can occur in the submucosal or peribronchial lymphatics; (4) in addition, one can have detached floating fragments of tumor within the bronchial lumen from intraluminal polypoid tumors without attachment at the margin (Table 2). Patients with a microscopically positive margin who have tumor either in the peribronchial tissues or lymphatics seem to have a significantly worse prognosis than those with CIS alone.[2]

Squamous cell CIS is a preinvasive lesion that occurs within the mucosa of major bronchi, and except for cases detected in the setting of screening, it is most frequently an incidental histologic finding in association with invasive squamous cell carcinomas.[31] It is at the most severe end of the continuum of mild, moderate, severe dysplasia and CIS. This spectrum comprises a constellation of histologic changes including nuclear to cytoplasmic ratio, nuclear atypia, mitotic activity, and thickness of the cytologic changes within the bronchial mucosa. These changes are most often found at the spurs of bronchial bifurcation. In addition, changes from dysplasia/CIS to normal mucosa are often abrupt.[32]

One report suggests reasonable reproducibility between pathologists among the various categories of squamous preinvasive lesions in the 1999 and 2004 WHO classification when looking at photomicrographs and high power fields of selected lesions.[33] However, it can be difficult to separate severe dysplasia from CIS, particularly on a frozen section. Maygarden et al.[34] analyzed 405 cases in which frozen sections of bronchial margins were performed in 268 (66%) of cases. They found 90.6% true-negative cases, 16 true-positive cases (6.0%), 4 (1.5%) false-positive cases, and 5 (1.9%) false-negative cases. The false positives included squamous metaplasia that was called dysplasia/CIS (*n* = 1), radiation changes thought to be suspicious for carcinoma (*n* = 1), and benign peribronchial lymphocytes were misinterpreted as small cell carcinoma (*n* = 2). There was poor correlation between gross distance of tumor from the margin and whether the margin was positive. Hofman et al.[35] found a discrepancy between frozen section and final histology in 11 of 21 (52%) cases with positive bronchial margins. Also, false-negative bronchial margins were most often (9 of 15,

60%) of patients with peribronchial infiltration. Finally, Weisel et al.[36] found that frozen sections had 7 of 70 (10%) false-negative rate in patients who underwent sleeve resection of the main bronchus.

In 2005, Pasic et al.[37] from Amsterdam reported on 11 patients referred to their program (denominator unknown) for bronchoscopic follow-up after resection of Tis-1-2-3N0 NSCLC (10 squamous, 1 adenocarcinoma). These patients all had had negative frozen section evaluation of their bronchial margins at the time of resection but were found to have CIS on final pathology review of the bronchial margin. None of these patients received adjuvant therapy for their CIS, but all were followed closely by serial LIFE endoscopies and yearly high-resolution CT scans. Three of the 11 developed stump recurrence (28%) within 5 to 15 months of resection. Three more developed a new primary squamous cell cancer, away from the stump, within 11 to 28 months of resection. In this article, the authors introduced a new pathological subclassification of CIS that is said to be simple and reproducible and that appeared to better subdefine the risks of patients with CIS at the margin: (1) CIS-S with CIS confined only to the surface epithelium; (2) CIS-D with involvement of the surface epithelium and into the bronchial gland ducts but not deeper; (3) CIS-A where the changes involve the surface epithelium, the glandular ducts, and the glandular acini. In their limited series, all stump recurrences were seen in the three patients with CIS-A; none of the six patients with CIS-D or the two patients with CIS-S had stump recurrence.[37] Whether CIS-A could be interpreted as invasive cancer by some and thus account for its related propensity to develop stump recurrence is a possibility. The subclassification suggested by Pasic et al. and listed above is certainly intriguing and warrants further validation.

Recent reports suggest the possibility of selecting higher risk preinvasive lesions by using predictive molecular markers.[38] The use of such technology may also one day possibly help us better define the potential invasive behavior of CIS at bronchial stumps or elsewhere in our patients' airways.

CONCLUSIONS

CIS at the surgical bronchial margin is a rare reported event in our literature. As per the AJCC/UICC TNM definition, the presence of CIS at the margin is considered a positive microscopic margin (R1(is)). There seems to be little evidence to support this when resection has been undertaken for squamous pathology. Indeed, after resection for squamous cell cancer, in contrast to the other more common R1 types bronchial positive margins, the presence of CIS does not seem to negatively affect the prognosis after resection, and there is no evidence that adding treatment beyond initial resection favorably affects the prognosis of these resected lesions. There are insufficient data to comment or conclude on the significance of CIS at the margin of resections for nonsquamous histologies.

Analysis of the existing literature does not allow us to recommend any management guidelines when CIS is identified by frozen or permanent sections at the bronchial margin.

An improved pathologic subclassification of CIS at the margin may allow for better characterization of the behavior of these tumors and possibly a subset of CIS margins that we could consider for more or less aggressive management in the future. The now accruing IASLC Lung Cancer Staging Prospective Project will be collecting data elements pertaining to this question of CIS at the bronchial resection margin and may help to better determine an optimal approach to these patients in the future.[39]

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APPENDIX

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