Thoracic Lymphatic Involvement in Patients Having Pulmonary Metastasectomy

Incidence and the Effect on Prognosis

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Abstract: Mediastinal and hilar lymph node involvement are rarely reported in the literature concerning pulmonary metastasectomy. The first problem is to determine with accuracy the incidence and location of thoracic lymph node involvement in patients with lung metastases. Determination of the impact on survival of this type of lymphatic spread may contribute to assessing whether metastatic nodal disease identified preoperatively is an absolute contraindication to metastasectomy. Systematic mediastinal lymph node dissection has revealed a statistically significant difference in survival between patients with lymph node involvement and those without lymph node metastases. Videomediastinoscopy to identify involved mediastinal lymph nodes can be safely performed and may have a role in a more accurate staging of the metastatic disease. The authors conclude that attention should be paid to ensuring that we do not operate on patients in whom we will leave behind diseases that we cannot reach. The discovery of mediastinal lymph node involvement may also influence decisions with respect to postresection adjuvant therapy.

Key Words: Pulmonary metastasectomy, Lymphadenopathy, Lymphatic spread.

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Mediastinal and hilar lymph node involvement had infrequently been examined in the literature concerning pulmonary metastasectomy before 2000. In publications since 2000, among the prognostic factors considered, metastasis from pulmonary metastases to the pulmonary lymphatic drainage has increasingly been considered. The true incidence, the pattern of lymph node involvement, the clinical significance, and the pathologic and oncologic interpretation now need to be clarified. Consequently, to obtain information and gauge opinion in this respect, it is necessary to conduct the appropriate examination of clinical reports in which, apart from any other prognostic factors, the presence and significance of nodal involvement have been analyzed.

WHAT IS THE TRUE INCIDENCE OF THORACIC LYMPH NODE INVOLVEMENT?

The first problem is to determine the incidence of positive thoracic lymph nodes in patients with lung metastases. In the International Registry of Lung Metastases between 1991 and 1995 of 5206 patients, 4572 (88%) underwent a complete surgical resection of the metastases.[1] Data are available from this source on the incidence of lymph node involvement in a large number of patients. The primary tumor was epithelial in 2660 cases, sarcoma in 2173, germ cell in 363, and melanoma in 328. Metastases to hilar or mediastinal nodes were found in 5% of patients overall (239 cases), corresponding to 11% in germ-cell tumors, 8% of melanomas, 6% of epithelial metastases, and only 2% of sarcomas. This is the largest data set available nevertheless, there are some difficulties in interpreting these results:

1. There were 18 participating centers from nine different countries.
2. There was no uniform use of radiologic techniques or consistent preoperative evaluation to categorize hilar or mediastinal metastases.
3. Criteria for performing preoperative mediastinoscopy varied.
4. The practice of intraoperative nodal dissection also varied and was performed in less than 9% of the patients. In general, only suspicious lymph nodes were removed.

It follows from the means of collection of data, the variations in practice, and the low rate of nodal dissection, that this incidence rate might be an underestimate, a supposition supported by analysis of subsequently published case series specifically addressing this particular question among groups of patients in which there was a policy of nodal sampling or systematic dissection. More recent studies, particularly, in epithelial tumors, therefore permit better determination of the incidence of thoracic lymph node and its repercussion in long-term survival.

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TABLE 1. Incidence of Thoracic Lymph Nodes in Patients with Lung Metastases

Publication	Era	Primary	Patients	Nodal Spread	Percent
Loehe et al.[2]	1996–1998	Mixed	63	9	14
Saito et al.[3]	1990–2000	Colorectal	138	20	14
Ercan et al.[4]	1985–1999	Mixed	70	20	29
Pfannschmidt[5]	1996–2001	Mixed	245	80	33
Welter et al.[6]	1993–2003	Colorectal	169	28	17
Menon et al.[9]	2002–2005	Mixed	57	6	11
Weighted average					22

We have extracted data on the incidence of mediastinal nodal involvement in six publications from 2001 to 2007 (Table 1), which shows a weighted average of 22%. These are of course already selected patients under consideration for having pulmonary metastasectomy, so it is still likely to be an underestimate of the true pathologic potential for metastases to themselves metastasize. It seems likely that because these pulmonary metastases come from tumors that have *ipso facto* demonstrated their metastatic potential that the metastases will in turn behave like other invasive lung tumors and seed the draining lymph nodes.

Loehe et al.[2] studied prospectively 63 patients with lung metastases, most of them from primary epithelial malignancies, who underwent 71 resections, and systematic mediastinal lymph node dissection. In nine patients (14%), at least one mediastinal lymph node with malignant cells was found. In these patients selected for metastasectomy, none of the preoperative computed tomography chest scans reported suspicion of malignant involvement of mediastinal nodes. Saito et al.[3] reported data on 165 patients with colorectal carcinoma, who underwent pulmonary metastasectomy from 1990 to 2000 at eight institutions. Hilar or mediastinal lymph nodes dissection or sampling in 138 patients revealed metastases in 20 patients (14%). In 2004, Ercan et al.[4] published the experience gained from the study in 883 patients who underwent pulmonary metastasectomy. Among them, only 70 patients (8%), treated from 1985 to 1999, had concomitant complete lymphadenectomy. Lymph node metastases were found in 20 of the 70 patients (29%; N1 in 9, mediastinal N2 in 8, and both in 3).

More recently, several other studies make reference to the location and the incidence of nodal metastasis. Pfannschmidt[5] reported on 245 patients who underwent pulmonary resection of lung metastases from colorectal carcinoma, sarcoma, and renal cell carcinoma. Systematic mediastinal and hilar lymph node dissection revealed lymph node involvement in 80 patients (45 pulmonary and hilar metastases; 22 pulmonary, hilar, and mediastinal metastases; and 13 only mediastinal involvement without pulmonary and hilar spread). Welter et al.,[6] among 169 patients operated for pulmonary metastases of colorectal cancer, found 28 patients with thoracic nodal spread (10 intrapulmonary, 12 hilar, and 6 mediastinal). Menon et al. found clinically unsuspected nodal involvement in 6 of 57 at mediastinoscopy and recommend that this investigation should be performed in all patients.

It is said of sarcoma that because this cancer has a low propensity for lymphatic metastasis, local control in the lung can be achieved by repeated surgery. In Pfannschmidt's series, among 58 patients with 10 different histologic categories, all clearly identified as sarcoma and 19% (11 patients) had nodal metastases.

Because these data based on existing practice show that for one in five patients, pulmonary metastases have already metastasized to the lymph nodes draining the lung, this may be presented as an argument for prompt removal of all pulmonary metastases (in which the lung is the only known site of metastatic disease) to preempt spread. This view is expressed by Pfannschmidt, "If pulmonary and lymph node metastases are clinically important because they serve as a source of ongoing disease dissemination, early removal of such lesions may interrupt the cascade of metastatic cells derived from metastatic sites. Thus, surgery may be an important form of systemic therapy."[5] However, we know that longer survival after metastasectomy is consistently associated with longer intervals between resection of the primary cancer and metastasectomy. Therefore, it is open to question whether the hasty removal to prevent spread is going to be an overall effective treatment. The presence of metastatic disease in the nodes draining the lung indicates further dissemination and it may be that metastasectomy is unlikely to alter the course of the disease.[7] Therefore, what we need to determine is whether the presence of nodal disease is a contraindication to metastasectomy. We address this question next.

WHAT IS THE IMPACT ON SURVIVAL FOR PATIENTS IN WHOM PULMONARY METASTASES HAVE THEMSELVES METASTASIZED TO LYMPH NODES?

There have been many retrospective studies of surgical treatment for pulmonary metastases from colorectal cancer in which prognostic factors have been carefully investigated. In the report by Kondo et al.[8] in which data from 10 reported series are reviewed, regional lymph node involvement emerged as an important prognostic factor, in addition to the number of pulmonary metastases and serum carcinoembryonic antigen level. We have summarized data from five articles in Table 2 which provide data on the difference in prognosis with and without thoracic lymphatic involvement.[2–6]

TABLE 2. Effect of Lymph Node Involvement on Prognosis

Publication	Era	Node Negative	Survival Rate 5 yr	Survival Rate 10 yr	Node Positive	Survival
Loehe et al.[2]	1991–1998	53[a]	36[a]	26[a]	9	0.5 yr
Saito et al.[3]	1990–2000	118	49	46	20	0.5 yr
Ercan et al.[4]	1985–1999	50	48		20	5 yr (10%)
Pfannschmidt[5]	1996–2001	165	45[a]		80	—[b]
Welter et al.[6]	1993–2003	169	42		28	19%

Best estimates of comparable survival from published series in which nodal status is reported. Survival is variously reported as 3, 5, or 10 yr average or median survival. When the data are not provided in this form, best estimates have been obtained from graphical displays for purposes of comparison.

[a] Editor's best estimates from published data available including graphs.

[b] Data are subdivided according to N1, N2, N1 + N2.

To highlight two recent examples, among 245 patients who underwent pulmonary metastasectomy and systematic mediastinal lymph node dissection, Pfannschmidt[5] showed a statistically significant difference in survival between patients with lymph node involvement and those without lymph node metastases (median survival 63.9 months; with N1 disease, 32.7 months; with N1 + N2 disease, 20.6 months). Welter et al.[6] studied the prognostic impact of unexpected lymph node metastases in patients undergoing resection of pulmonary metastases from colorectal cancer and specified the influence of pulmonary and mediastinal nodal involvement. The survival difference between pulmonary (86 months) and hilar/mediastinal metastases (25 and 35 months) was statistically significant. Five-year survival with pulmonary, hilar, and mediastinal metastases was 78.5, 0, and 0%, respectively.

Given these differences that are large and consistent in Table 2, a clear case can be made for better preoperative evaluation. In the study by Menon et al.,[9] they reported that videomediastinoscopy identified involved mediastinal lymph nodes in 6 of 57 patients undergoing pulmonary metastasectomy, most of them from colorectal cancer.

The hidden nature of nodal involvement and its powerful effect on prognosis probably applies to all cancer types in which pulmonary metastasectomy is considered. Khan et al.[10] have studied the role of surgery in pulmonary metastases of endocrine origin. None of the surgical patients had any radiographic evidence of mediastinal disease preoperatively. Mediastinoscopy was not performed in any patient. At the time of surgery, mediastinal lymph node sampling was performed. Patients without mediastinal nodal involvement and those with a longer duration before development of pulmonary metastases had the best prognosis.

WHAT IS CURRENT PRACTICE OF LYMPH NODE ASSESSMENT AND DISSECTION?

In a recent European Society of Thoracic Surgeons survey,[11] the presence of clinically positive lymphadenopathy is believed to be a relative contraindication to pulmonary metastasectomy by 64%, whereas biopsy proven or pathologically positive mediastinal nodes constitute an absolute (64%) or relative (32%) contraindication for most of the observed population. Nevertheless, a systematic assessment of mediastinal nodes before lung metastasectomy is apparently an uncommon practice. Most of the responders rarely (43.8%) or never (24%) perform mediastinoscopy, whereas another 28.8% state that this is done only "sometimes," and usually because of increased suspicion by preoperative imaging tests. Only 3.4% of responders consistently verified mediastinal lymph nodes by mediastinoscopy (2% usually and 1.4% always) before selecting a patient for surgical resection. At the time of pulmonary metastasectomy, roughly half (55.5%) of the responding surgeons perform mediastinal lymph nodal sampling, whereas 13% perform a complete mediastinal lymphadenectomy. One in three surgeons (32.2%) performs no lymph node biopsy whatsoever.

After this analysis, we agree with the editorial comment of Treasure[7] in relation to this problem: "If the benefit we offer is that we cure some and that these are the only ones who benefit, then we should pay great attention to ensuring that we do not operate on patients in whom we will leave behind disease we cannot reach, because at present there may be 10% of patients who could be spared this unavailing lung resection if we were to stage the mediastinum. We should pay great attention to ensuring that we do not operate in patients in whom we will leave behind disease we cannot reach."

CONCLUSIONS

1. The incidence of lymphatic spread from the pulmonary metastases to the usual lymphatic drainage of the lung is common, probably more common than generally recognized. Patients are highly selected for metastasectomy so the reports based on surgical series will be an underestimate but of patients with unsuspected nodal involvement, and recurrent cancer clinically only involving the lung, more than a fifth have thoracic nodal disease. Furthermore, this seems to occur irrespective of the type of primary cancer.
2. Patients who have mediastinal nodal disease have a much worse survival than those whose nodes are clear. This has been clearly shown and is not surprising.
3. We concur with the views of several authors of these reports, and with Treasure's editorial, that best practice would be to exclude, as far as possible, patients with thoracic nodal involvement from pulmonary metastasec-

tomy with intent to cure. At present, mediastinoscopy seems to be the most effective way of achieving this.

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