The role of lymphadenectomy during lung metastasectomy

Jon Zabaleta, Borja Aguinagalde, Iker López, Arantza Fernandez-Monge, José Miguel Izquierdo

Thoracic Surgery Department, Basque Health Service, Donostialdea Integrated Health Organisation, San Sebastian, Spain
Contributions: (I) Conception and design: J Zabaleta, B Aguinagalde; (II) Administrative support: All authors; (III) Provision of study material or patients: I López; (IV) Collection and assembly of data: A Fernandez-Monge, JM Izquierdo; (V) Data analysis and interpretation: B Aguinagalde, J Zabaleta; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
Correspondence to: Jon Zabaleta. Donostia University Hospital, Paseo Dr Beguiristain s/n, 20014 Donostia, Spain. Email: jon.zabaletajimenez@osakidetza.eus.

Abstract: Lymph node involvement implies the presence of two routes of dissemination in patients with lung metastasis. For this reason, we assessed its impact on patients undergoing surgery for lung metastasis. In this review, we have sought to summarise the results of studies analysing the presence of thoracic lymph node involvement in patients who have undergone surgery for lung metastasis from different points of view: its impact on survival, the risk factors for developing lymph node metastasis, the attitude of surgeons towards lymphadenectomy in this population, the safety of systematic lymphadenectomy and the impact of systematic lymphadenectomy on survival.

Keywords: Lung metastases; lung metastasectomy; pulmonary metastasectomy; lymphadenectomy; survival; prognostic factors

Introduction

Systematic mediastinal lymphadenectomy or sampling is routinely performed for primary neoplasm of the lung, including adenocarcinoma, squamous cell carcinoma and neuroendocrine tumours (1). Despite a paucity of randomized clinical trial data, it is now generally accepted that overall survival for many tumour types is improved with resection of limited metastases in carefully selected patients (2). Nonetheless, controversy exists surrounding the need for assessment of mediastinal lymph nodes during pulmonary metastasectomy (1). Given the current understanding of tumour biology, it is assumed that metastases to thoracic lymph nodes would convey a worse prognosis. The lungs are an ideal metastatic goal for haematogenously disseminated tumours due to their nature: cells from the lung parenchyma are very close to the vascular space (it being an end organ with small capillaries) and it is a nutrient-rich environment where there is a very good supply of both blood and oxygen (3). Additionally, the lungs produce certain cytokines (e.g., CXCL12) that are responsible for initiating the signalling for leukocytes, neutrophils and other effector cells that induces their movement from the blood towards sites of infection or tissue damage (3). For this reason, lymph node involvement implies the presence of two routes of dissemination, haematogenous and lymphatic, and hence, overall and disease-free survival rates are expected to be poorer in patients with mediastinal lymph node involvement (3-5).

Strengths and weaknesses of the international registry of lung metastasis

Over recent years, since Pastorino published the results of the International Registry of Lung Metastasis in 1997 (2), resection of lung metastasis from primary non-pulmonary cancer has become an essential part of the activity of thoracic surgery departments (6). While we are still waiting for the results of the first clinical trial on lung metastasis (PulMIC trial) (7), several case series (8,9) and meta-analyses (10,11) have focused on the factors that affect survival following metastasectomy seeking to bring the list of factors proposed by Pastorino up to date. At present, the three factors suggested in 1997 seem to remain valid: status

of surgical margins, disease-free interval and number of lung metastases.

The registry has some limitations, however, for analysing the effect of lymph node involvement on survival (12): data were gathered on patients from 18 countries, preoperative radiological techniques differed between hospitals, as did the indications for preoperative mediastinoscopy, and lymphadenectomy was only performed in 4.6% of cases (2).

Given all of this, we wanted to analyse studies published in recent years to further explore the role of lymphadenectomy in patients who undergo surgery for lung metastasis.

Impact of thoracic lymph node involvement on survival following lung metastasectomy

As we have indicated above, lymph node involvement implies the presence of two routes of tumour dissemination, and given this, it is not surprising that patients with lymph node involvement have lower survival rates. Numerous retrospective studies based on patients who have undergone surgery for lung metastasis from colorectal cancer published in recent years refer to the impact of lymph node involvement on survival (8-11). On the one hand, some studies such as that of Nanji et al. (13) observed a negative effect on survival. After studying 420 patients, they concluded that lymph node involvement was the best prognostic factor [hazard ratio (HR) 2.08; 95% CI, 1.41–3.07]. Renaud et al. (14) reported similar results in their study of 320 patients who underwent systematic lymphadenectomy. Specifically, they observed that patients with no lymph node involvement survived twice as long as those with lymph node involvement (median survival 94 months versus 42 months in patients with positive lymph node involvement). On the other hand, we have also found studies that did not find significant differences, such as those of Sponholz et al. (15) and Kumar et al. (16). Sponholz studied 54 over-70-year-old who underwent surgery in Germany, and the only factors that reached significance were disease-free interval and anatomic resection (15), while Kumar analysed 71 patients who underwent surgery in India, and concluded that in their series, the only variables with an impact on survival were a history of extra-pulmonary metastasis and local lymph node invasion at the time of the primary tumour surgery (16). Taking broader view, we found research analysing metastases from kidney cancer (17), which observed a clear tendency towards a poorer survival rates with increasing lymph node stage, with mean survival times of 71.9, 50.7 and 36 months in patients with N0, N1

and N2 disease, respectively (17). Pfannschmidt et al. (18) also found similar results analysing survival after systematic lymphadenectomy in 245 patients with metastasis from colorectal cancer, kidney cancer or sarcoma (18).

In a meta-analysis published in 2013, Gonzalez et al. (10) analysed papers published between 2000 and 2011 assessing survival following the removal of pulmonary metastasis from colorectal cancer and based on more than 40 patients. They included 25 publications with data on a total of 2,925 patients. Pooled HRs were calculated using a random effects model for parameters considered potential prognostic factors. Four parameters were associated with poor survival:

(I) A short disease-free interval between primary tumour resection and development of lung metastases (HR 1.59; 95% CI, 1.27–1.98);
(II) Multiple lung metastases (HR 2.04; 95% CI, 1.72–2.41);
(III) Positive hilar and/or mediastinal lymph nodes (HR 1.65; 95% CI, 1.35–2.02);
(IV) Elevated prethoracotomy carcinoembryonic antigen (HR 1.91; 95% CI, 1.57–2.32).

More recently, a recently reported meta-analysis of individual data from papers published between 2007 and 2014 (11) has analysed individual data from 3,501 patients from 17 studies. The objective of this meta-analysis was to assess the impact of previous liver metastasectomy on survival following lung metastasectomy. In individual data meta-analysis using multilevel random effects, it was observed that the variable with the greatest impact on survival was lymph node involvement, with an HR of 1.83 (95% CI, 1.44–2.32). Adding to the variables with a negative impact on survival identified by Gonzalez (10), this study identified previous liver metastasis, positive surgical margins and size of the metastases (11).

Given all this, it is not surprising that reviews, such as that published by Chakedis and Schmidt in 2018 (19), list lymph node involvement among the risk factors for poor prognosis.

Current attitude of thoracic surgeons towards systematic lymphadenectomy in patients with lung metastasis

To assess the variability in the indications and types of surgery carried out in patients with lung metastasis, the Pulmonary Metastasectomy Working Group of the European Society of Thoracic Surgeons (ESTS) decided to carry out a survey among its members to gather data on

current daily practice in surgery for lung metastasis (20). For this purpose, they developed a questionnaire of 39 questions and it was completed by 200 thoracic surgeons. In this questionnaire, there were three questions that address the topic of lymphadenopathy:

(I)   Asked about indications or contraindications, 64% of respondents reported that the presence of mediastinal lymph node involvement was an absolute contraindication to metastasectomy and 32% considered it to be a relative contraindication. Only 4% of the participating surgeons considered that mediastinal lymph node metastasis was not a contraindication (20);

(II)   Regarding lymph node status prior to surgery, only 3.7% of respondents claimed that they performed mediastinoscopy (1.4%, always and 2%, regularly), while 43.8% reported performing it rarely and 24% not at all (20);

(III) Concerning the surgical procedure itself, a third of the surgeons that responded (32%) reported not doing any type of lymphadenectomy, while 55.5% of them took a sample and only 13% carried out complete mediastinal lymphadenectomy (20).

More recently, in 2013, Embun et al. published a prospective study with the largest number of patients undergoing surgery for lung metastasis from colorectal cancer reported to date. They included 543 patients, from 35 different hospitals, who underwent surgery between 2008 and 2010, providing a relatively up-to-date picture of the characteristics of operated cancer patients and the surgical technique used (21). Overall, only 9% of the patients underwent systematic lymphadenectomy (21) and 52% of the interventions did not include any lymphadenectomy (21). To our knowledge, the most up-to-date and geographically broad analysis of current trends is found in the systematic review and meta-analysis of individual data published by Zabaleta et al. (11) in 2018. This study analysed data from 17 studies from nine different countries, and out of the 3,500 patients included in the study, there were no data on the status of the lymph nodes in 1,405 patients, implying that 41% of patients who underwent surgery did not undergo any type of lymphadenectomy (11).

Risk factors for developing lymph node metastasis

Given a lack of homogeneity in patient characteristics between studies and that lymphadenectomy is not performed systematically, to estimate the real percentage of patients with lymph node involvement and attempt to determine risk factors for lymph node dissemination, we have to rely on data from groups that do perform systematic lymphadenectomies. In 2014, Bölükbas et al. published the results of analysing surgery performed in 165 patients with pulmonary metastasis from colorectal cancer. In this review, they found a prevalence of lymph node metastases of 22.4% (22). The risk factors for developing lymph node metastasis were: number of pulmonary metastases, the primary cancer being rectal and extent of the resection procedure being greater than a wedge resection (that is, segmentectomy or lobectomy). A striking finding in this study was that there was a group of 17 patients with 4 or fewer pulmonary metastases who underwent atypical lung resection, none of whom had lymph node involvement (22).

A year later, Seebacher et al. published a study based on 313 metastasectomies from different types of cancer (23). In this case, the authors focused on unexpected metastases (unlike Bölükbas et al. who also included those detected in the preoperative assessment). Unexpected metastasis was found in 35.5% of patients with metastasis from breast cancer, 9.2% of those with metastasis from colorectal cancer and 20.8% of those with metastasis from kidney cancer (23). It is important to note that, in this series, only 10.5% of patients underwent preoperative positron-emission tomography and when findings of this imaging or computed tomography were positive, endobronchial ultrasound or mediastinoscopy were performed. The prognostic factors for developing lymph node involvement identified in this series were: a greater number of metastases and tumour diameter of more than 4 cm (23).

In 2018, Ali published a study on 160 patients who underwent surgery for lung metastasis from colorectal cancer, where lymphadenectomy was only performed if positron-emission or computed tomography findings suggested lymph node involvement or if the lymph nodes were found to be enlarged during surgery (24). Lymph nodes resected during surgery and those in which disease was detected during the postoperative follow-up were considered positive. Out of all 160 patients, 60 underwent lymphadenectomy, with positive findings in 8% of cases (5 patients) and among the other 100 patients, 23% (23 patients) developed lymph node involvement during follow-up. A larger number of pulmonary metastases and the primary cancer being in the colon were factors associated with a higher probability of developing mediastinal lymphadenopathies. A trend was observed in patients with

Table 1 Risk factors for developing lymph node metastasis

Author	Year	Country	Number of patients	Systematic lymphadenectomy (%)	Risk factor
Ali	2018	Republic of Korea	160[a]	37.5	Number of lung metastases
					Primary colon cancer
Bölükbas	2014	Germany	165[a]	100	Number of lung metastases
					Primary rectal cancer
					Lobectomy or segmentectomy
Seebacher	2015	Germany	209[b]	100	Greater number of lung metastases
					Tumour diameter >4 cm

[a], all patients with primary colorectal cancer; [b], patients with primary colorectal, breast or kidney cancer.

Figure 1 Lymphadenectomy after lung metastasectomy (33). Available online: http://www.asvide.com/article/view/32480

a history of liver metastasis and larger metastases, but the differences did not reach statistical significance (24). *Table 1* summarises the findings of these three studies.

The origin of primary tumours may also affect the likelihood of lymph node involvement, as demonstrated by Welter *et al.* (25). They studied growth characteristics of different metastasis subtypes in the lung, and found that patients with metastases from melanoma showed an increased possibility of lymphangitic spread (27.8%). Sarcoma metastases had the lowest incidence of lymphangitic spread (3.5%), and patients with colorectal carcinoma or renal cell carcinoma mestastes intermediate risk for lymph node disease (18.0% and 18.9% respectively) (25).

Safety of systematic lymphadenectomy

It should not be forgotten that when we say that systematic lymphadenectomy is a safe procedure, this does not mean that

it is risk free (26). Few studies have analysed the impact of lymphadenectomy on postoperative complications due to lung metastases, but we could extrapolate from research assessing lymphadenectomies for the treatment of stage 1 lung cancer, given that these cases in principle would involve tumours of less than 4 cm in diameter and no lymph node involvement (27).

Watanabe *et al.* summarised the complications observed after lymphadenectomy by video-assisted thoracoscopy surgery in patients with early-stage lung cancer (26). In association with the lymphadenectomy, they observed chylothorax, recurrent paralysis, heart arrhythmia and pleural effusion (26). Analysing studies that only include stage I patients (28-32), authors reported complications related to the lymphadenectomy in between 6.3% and 13.8% of patients, the most common being heart arrhythmia (26).

Regarding research assessing survival in patients who underwent systematic lymphadenectomy, Renaud *et al.* also reported 5% of recurrent paralysis after surgery (14). Comparing series of patients who did and did not undergo lymphadenectomy in terms of complications, we can observe a slightly higher rate in those in whom this technique was performed: 14–23% (15,32) versus 4–8% patients in whom it was not performed (9,16) (*Figure 1*). These data must be interpreted with caution, however, since lymphadenectomy is not the only cause of complications, and series with a higher rate of wedge resections are more likely to have a lower rate of complications (for a more comprehensive picture see the data summarised in *Table 2*).

Does systematic lymphadenectomy improve survival?

This question is very difficult to answer. As we have

Table 2 Complications observed

Author	Year	Number of patients	Systematic lymphadenectomy (%)	Wedge resection (%)	Positive lymph node involvement (%)	Complications (%)
Okumura	2017	785	12	60	5	8
Kumar	2018	71	0	85.9	2.8	4.2
Sponholz	2018	224	100	30	23.6	23
Bolukbas	2014	165	100	33.9	22.4	13.9

indicated, numerous factors have an impact on survival after pulmonary metastasectomy and it is difficult to compare different case series given that selection criteria may vary between research groups. Papers such as that published by Call *et al.* entitled, "*Impact of inappropriate lymphadenectomy on lung metastasectomy for patients with metastatic colorectal cancer*" may suggest the answer. This study analysed survival as a function of whether or not patients underwent lymphadenectomy (34). After analysing 522 patients of whom 48% underwent some type of lymphadenectomy (systematic, sampling, and minor lymphadenectomy in 20%, 34.8% and 45% of patients respectively), the authors observed that 44% of patients who did not undergo lymphadenectomy survived at least 5 years, while of 5-year survival rate in those who did undergo lymphadenectomy was 58.3% or 24.8% respectively depending on whether or not there was lymph node involvement (34). They did not, however, analyse survival stratifying by whether or not systematic lymphadenectomy was performed, which is what would really provide an answer to the question posed above. If we compare the two study groups (34) using the data published on the Kaplan-Meier survival estimates at 60 and 70 months, patients who did not undergo lymphadenectomy had probabilities of survival of 39% and 15%, respectively, compared to 41.60% and 13%, for patients who underwent lymphadenectomy (34).

Hamaji *et al.* also analysed survival depending on whether or not systematic lymphadenectomy was performed in their study entitled "*Is lymph node dissection required in pulmonary metastasectomy for colorectal adenocarcinoma?*" (35). They analysed data from 518 patients, of whom 199 did not undergo any type of lymphadenectomy and 319 patients who did undergo lymphadenectomy. The 5-year survival rate was 47.1% in all patients, 48.3% in those who did not undergo lymphadenectomy, 49.3% in those who underwent lymphadenectomy and had no lymph node involvement,

and 20% in those who underwent lymphadenectomy and did have lymph node involvement (35). In this paper, they conclude that the performance of lymphadenectomy can be recommended for prognostic purposes, although it does not improve survival. *Table 3* lists some of the papers mentioned in this review, together with the reported survival rates and percentages of patients undergoing lymphadenectomy.

Before finishing this section, we would like to recall that there are no current consensus guidelines for deciding whether patients undergoing metastasectomy require adjuvant therapy (19), unlike in the case of those with primary lung cancer (36). In fact, in a paper published by Al-Almeri (8), in which patients were stratified by risk, low, medium and high (based on the criteria of Okumura), it was found that 17%, 18% and 29%, respectively received chemotherapy, when it would be logical to expect that the low-risk group would receive less adjuvant treatment than the others. Additionally, it was found that, within each risk group, survival did not vary between those who were and were not given chemotherapy (8).

Conclusions

Thoracic lymph node involvement during surgery for lung metastasis is a negative prognostic factor. Despite the fact that systematic lymphadenectomy is a safe procedure, it is not complication free and increases surgical times. There is no scientific evidence that systematic lymphadenectomy improves the survival of patients with pulmonary metastases. We recommend performing this procedure systematically in centres seeking to investigate predictors of pulmonary metastases, given that not studying the lymph nodes might lead to their being insufficient data on a significant confounding factor. Nonetheless, we must always properly inform patients that the goal of lymphadenectomy is to estimate their prognosis as

Table 3 Survival and percentage of patients with no lymph node assessment

Author	Number of patients	Systematic lymphadenectomy (%)	Wedge resection (%)	Positive lymph node involvement (%)	No lymph node assessment (%)	5-year survival (%)
Okumura	785	12	60	5	40	65.1
Kumar	71	0	85.9	2.8	84	51.9
Sponholz	224	100	30	23.6	0	46
Bolukbas	165	100	33.9	22.4	0	54
Al-Ameri	756	NR	81	NR	NR	56
Nanji	420	NR	57	13	37	40
Renaud	320	100	71	44	0	22.5
Pfannchmid	245	100	59	15.7	0	Median: 42.4 months
Zabaleta	3,501	NR	NR	19.1	41	51.9

NR, not reported.

accurately as possible rather than to improve survival.

Footnote

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