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Should mediastinal lymphadenectomy be performed during lung metastasectomy of renal cell carcinoma?

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Abstract

A best evidence topic was constructed according to a structured protocol. The question addressed was whether radical mediastinal lymphadenectomy should be performed during lung metastasectomy of renal cell carcinoma (RCC). Of the 13 papers found through a report search, seven represent the best evidence to answer this clinical question. The authors, journal, date, country of publication, study type, group studied, relevant outcomes and results of these papers are given. We conclude that on the whole, the seven-retrieved studies support the realization of systematic radical mediastinal lymphadenectomy. The published literature showed a prevalence of lymph node involvement (LNI) that approaches 30%. The majority of the studies conclude that LNI is a significant, independent prognostic of survival. Indeed, some authors did not report any 5-year survival in the case of LNI. On the contrary, however, a 5-year survival of ~50% was reported when no LNI was present. To date, the published data do not allow conclusions to be drawn regarding the prognosis of hilar vs mediastinal LNI: only one paper focused on the difference between hilar and mediastinal location and showed no difference. In addition, only one study has compared the survival of patients with or without lymphadenectomy, showing greater survival when mediastinal lymphadenectomy was performed. Despite the poor prognosis of patients with LNI, surgery seems to be the best treatment for potentially curative RCC with metastases. It is known that RCC metastases do not respond well to chemotherapy and radiotherapy. Indeed, reported 5-year survival rate ranged between 3 and 11% for non-operated patients. Consequently, resection must be as complete as possible and include a systematic total mediastinal lymphadenectomy, which will probably yield better loco-regional control and evaluation of prognostic factor. However, the published evidence remains quite limited and mainly based on retrospective studies on highly selected patients, with a low level of evidence. Indeed, most patients referred to surgery are younger, fitter, and have fewer metastases. Consequently, the survival gain could be biased, related more to the resectability and the good performance status rather to the resection itself. Consequently, although these preliminary results are interesting, they must be interpreted with caution.

Keywords: Lymphadenectomy • Mediastinum • Metastases • Renal cell carcinoma • Thoracic

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. The protocol is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients undergoing lung metastasectomy of renal cell carcinoma] does [lymphadenectomy] improve [survival]?

CLINICAL SCENARIO

You are assessing a 68-year old patient for surgical management of metachronous lung metastases of a renal cell carcinoma (RCC). The chest computed tomography (CT) scan detects two peripheral metastases of 18 and 16 mm in the upper left lobe, with mediastinal nodes in stations 5 and 7, one measuring 12 mm. The positron emission tomography CT shows a hyper-signal on the lesions but not on the mediastinal lymph nodes, and there is also no sign of abdominal recurrence or metastases elsewhere. You decide to perform wedge resections of the two lesions in the upper left lobe. From a radiological point of view, the nodes on the chest CT do not seem suspect. You wonder whether a lymph node sampling would be more appropriate than a radical mediastinal lymphadenectomy (especially due to the risk of injury to the recurrent laryngeal nerve). You, therefore, decide to consult the published evidence concerning the role of mediastinal lymphadenectomy during lung metastasectomy of RCC.

SEARCH STRATEGY

Medline 1998–2012 using the OVID PubMed, Pascal and Cochrane interfaces, with results limited to English language articles: (Mediastinal lymphadenectomy.mp) AND (metastases.mp) AND (renal cell carcinoma.mp). A manual search was then used to follow up on the references from the retrieved studies.

Table 1: Overview of the studies

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Murthy *et al.* (2004), Ann Thorac Surg, USA [2]	92 patients undergoing pulmonary metastasectomy of RCC	Prevalence of LNI	N+: 12 of 32 patients (37.5%) Location: 50% mediastinal (N2–N3)	No impact of the number of lymph nodes dissected on survival
		Survival	Median follow-up (years): 3.7 ± 3.1 OS: significantly lower in case of LNI In case of CR: 3 LNI: 30% 2 LNI: 45% 1 LNI: 55% 0 LNI: 65% ($P = 0.004$)	
Prospective study (level 2C)	Histological data available for 32 patients (34.8%)			Small number of patients for whom the histological data are available
		Morbidity	None related to lymphadenectomy	
Kanzaki *et al.* (2010), Eur J Cardiothorac Surg, Japan [3]	48 patients (59 thoracotomies) for lung metastases of RCC	Prevalence of LNI Recurrence	N+: 5 of 48 patients (10.4%) 4 patients (8.3%)	No information on the type of lymphadenectomy performed (sampling or radical?)
Retrospective study (level 3C)	Exclusion of patients when LNI is suspected on the preoperative CT scan			
Plitz *et al.* (2002), Ann Thorac Surg, Germany [4]	105 patients (150 thoracotomies) for lung metastases of RCC	Survival	Five-year OS: pN0: 48% pN+: 0%	No data on the prevalence of LNI
Retrospective study (level 3C)		Prognostic variable of survival	LNI: independent prognostic factor ($P = 0.0016$, RR: 2.42, OR: 1.40–4.20)	
		Morbidity	One recurrent laryngeal nerve paralysis (0.95%)	
Pfannschmidt *et al.* (2002), Ann Thorac Surg, Germany [5]	191 patients (248 thoracotomies) for lung metastases of RCC	Prevalence of LNI Prognostic variable of survival	N+: 57 of 191 patients (29.9%) LNI: independent prognostic factor ($P = 0.0038$)	No difference found between mediastinal or hilar nodal involvement ($P = 0.54$)
Retrospective review (level 3C)		Survival	Three-year OS: 31.4% (N+) vs 55.4% (N0)	Retrospective study
		Morbidity	One oesophageal perforation (death on day 29)	
Assouad *et al.* (2007), Ann Thorac Surg, France [6]	65 patients undergoing lung metastasectomy for RCC	Prevalence of LNI	N+: 13 of 44 patients (29.5%); N1: 6 (46.2%); N2: 7 (53.8%)	Retrospective study
		Survival	5-year OS: pN+: 0% pN−: 52%	
Retrospective study (level 3C)	Radical mediastinal lymphadenectomy performed in 67.7% of patients (44 of 65 patients)	Prognostic variable of survival	LNI: independent prognostic factor ($P = 0.0018$)	
		Morbidity	None related to lymphadenectomy	
Winter *et al.* (2010), J Urol, Germany [7]	110 patients (156 thoracotomies) undergoing lung metastases for RCC	Prevalence of LNI	N+: 38 of 110 patients (34.5%); N1: 8 (7.3%), N2: 17 (15.5%), both N1 and N2: 13 (11.8%)	Retrospective study
Retrospective review of a prospective database (level 3C)		Prognostic variable of survival	Univariate analysis: Mean survival of pN0: 102.2 months, pN+: 19.1 months (pN2: 13.8 months, pN1: 28.9 months) ($P < 0.001$)	

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
			Multivariate analysis: LNI is a prognostic factor: (RR: 5.8; CI: 2.5–13.3)	
		Historical comparison	Better OS in case of lymphadenectomy (HR: 0.66; CI: 0.41–1.06; $P = 0.08$)	
		Morbidity	One recurrent laryngeal nerve paralysis (0.9%) and one chylous leak (0.9%)	
Meimarakis *et al.* (2010), Am J Surg, Germany [8] Retrospective review of a prospective database (level 3C)	202 patients with lung metastases of RCC 91 radical mediastinal lymphadenectomies (45%)	Prevalence of LNI Survival rate	N+: 27 of 91 patients (30%) pN+: 19.1 (CI: 5.8–32.4) months vs pN0: 92.0 (CI: 35.7–148.2) months; ($P < 0.001$)	Retrospective study
		Prognostic variable of survival	LNI: independent prognostic factor (HR: 3.6; CI: 1.5–8.4; $P < 0.004$)	
		Morbidity	None related to lymphadenectomy	

CI: confidence interval; CR: complete resection; HR: hazard ratio; LNI: nodal involvement; OR: odds ratio; OS: overall survival; RCC: renal cell carcinoma; RR: relative risk.

SEARCH OUTCOME

A total of 13 papers were identified using the reported search strategy, from which three represented the best evidence to answer the question. Four other articles were found using the references of the selected articles. Papers that were not written in English and that do not provide data on lymphadenectomy during lung metastasectomy of RCC, as well as case reports, were excluded. The seven papers are summarized in Table 1 [2–8].

RESULTS

Murthy *et al.* [2] reported their experience with 92 patients who underwent a lung resection for RCC metastases. Even if the histological data were only available for 35% of the patients, lymph node involvement (LNI) was present in ∼40% of these patients, with mediastinal involvement in half of the cases. The LNI was a strong prognostic factor of survival ($P < 0.01$). Indeed, the percentage of survival significantly decreased with the number of lymph nodes affected: 65% in the absence of LNI vs 30% when three nodes were involved, with a median follow-up of 3.7 years. In a smaller study, Kanzaki *et al.* [3] reported a prevalence of LNI approaching 11%, although the authors had preoperatively attempted to exclude patients suspected of having LNI. However, the authors did not explain which kind of lymphadenectomy was performed (sampling or systematic total lymphadenectomy). In a paper on 105 patients, Plitz *et al.* [4] reported a 5-year survival rate of 0% when LNI was detected, vs 48% if no LNI was assessed by histology. The multivariate analysis showed that LNI was an independent prognostic factor of survival ($P = 0.0016$). In a trial performed on 191 patients, Pfannschmidt *et al.* [5] reported an LNI rate of 30%. This study was in line with the previous papers, illustrating a better survival rate in the absence of LNI (31.4 vs 55.4%; $P = 0.0038$). This was confirmed by the multivariate analysis, which showed that LNI was an independent prognostic factor of survival ($P = 0.0038$). However, the authors did not find any differences concerning the mediastinal or hilar nodes involved. Assouad *et al.* [6] reported their experience with 65 patients, of which 67% had undergone a radical mediastinal lymphadenectomy. The prevalence of LNI was ∼29.5%, without any difference between hilar and mediastinal nodes. There was no 5-year survival in case of LNI, while more than half of the patients were still alive if no LNI was detected. The multivariate analysis showed LNI as an independent prognostic factor of survival ($P = 0.0018$). In a retrospective review of 110 patients, Winter *et al.* [7] reported a prevalence of LNI approaching 35%, with twice as much mediastinal involvement than hilar involvement. They showed, using univariate and multivariate analyses, that LNI was an independent prognostic factor of survival. In addition, they compared these patients to a historical series composed of 111 patients with lung metastases of RCC who did not benefit from a mediastinal lymphadenectomy. Although non-significant ($P = 0.08$), they did find a better rate of survival in the case of lymphadenectomy (hazard ratio (HR): 0.66; CI: 0.41–1.06). In a study based on 202 patients, of whom 45% benefitted from a mediastinal lymphadenectomy, Meimarakis *et al.* [8] reported a prevalence of LNI of ∼30%. A significantly lower survival rate was found in the case of LNI ($P < 0.001$), which was confirmed by the multivariate analysis and which found LNI to be an independent prognostic factor ($P < 0.004$).

CLINICAL BOTTOM LINE

Although the low level of evidence of several papers on metastasectomy, including Treasure *et al.* [9], prevented the ESTS working group from setting firm recommendations regarding metastasectomy [10], our work on the role of systematic radical mediastinal lymphadenectomy during lung metastasectomy of RCC clearly makes us in favour of it. Most of the studies show a prevalence of LNI of ~30%, with a mediastinal location in half of the cases. Consequently, not performing lymphadenectomy exposes patients to the risk of failing to achieve a complete carcinological resection and loco-regional recurrence. All the papers conclude that LNI is a significant independent prognostic factor of survival. To date, the published data do not allow any conclusion to be drawn regarding the prognostic of hilar vs mediastinal LNI: only one paper focuses on the difference between hilar and mediastinal location, and does not report any difference. In addition, only one study compares the survival of patients with or without lymphadenectomy, and concludes in favour of mediastinal lymphadenectomy. Despite the poor prognosis of patients with LNI, surgery seems to be the best treatment of potentially curative RCC with metastases. It is known that RCC metastases do not respond well to chemotherapy and radiotherapy. Indeed, the reported 5-year survival rate ranged between 3 and 11% for non-operated patients [9], while it varied from 21 to 60% in most surgical series [11–16]. Therefore, although consensus has yet to be reached [17], metastasectomy for lung metastases of RCC seems to be the best treatment for selected patients with resectable disease. Consequently, the resection must be as complete as possible and include a total systematic mediastinal lymphadenectomy (even if imaging is not in favour of such invasion), which will probably yield a better loco-regional control and evaluation of prognostic factor. However, the literature is quite limited and of low-level evidence. In addition, most patients referred for surgery are younger and fitter patients with fewer metastases. Consequently, the survival gain could be biased, related more to the resectability and the good performance status rather to the resection itself [18]. Further studies are necessary to confirm these results.

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REFERENCES

[1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. Interact CardioVasc Thorac Surg 2003;2:405–9.
[2] Murthy SC, Kim K, Rice TW, Rajeswaran J, Bukowski R, DeCamp MM *et al.* Can we predict long-term survival after pulmonary metastasectomy for renal cell carcinoma? Ann Thorac Surg 2005;79:996–1003.
[3] Kanzaki R, Higashiyama M, Fujiwara A, Tokunaga T, Maeda J, Okami J *et al.* Long-term results of surgical resection for pulmonary metastasis from renal cell carcinoma: a 25-year single-institution experience. Eur J Cardiothorac Surg 2011;39:167–72.
[4] Piltz S, Meimarakis G, Wichmann MW, Hatz R, Schildberg FW, Fuerst H. Long-term results after pulmonary resection of renal cell carcinoma metastases. Ann Thorac Surg 2002;73:1082–7.
[5] Pfannschmidt J, Hoffmann H, Muley T, Krysa S, Trainer C, Dienemann H. Prognostic factors for survival after pulmonary resection of metastatic renal cell carcinoma. Ann Thorac Surg 2002;74:1653–7.
[6] Assouad J, Petkova B, Berna P, Dujon A, Foucault C, Riquet M. Renal cell carcinoma lung metastases surgery: pathologic findings and prognostic factors. Ann Thorac Surg 2007;84:1114–20.
[7] Winter H, Meimarakis G, Angele MK, Hummel M, Staehler M, Hoffmann RT *et al.* Tumor infiltrated hilar and mediastinal lymph nodes are an independent prognostic factor for decreased survival after pulmonary metastasectomy in patients with renal cell carcinoma. J Urol 2010;184:1888–94.
[8] Meimarakis G, Angele M, Staehler M, Clevert DA, Crispin A, Rüttinger D *et al.* Evaluation of a new prognostic score (Munich score) to predict long-term survival after resection of pulmonary renal cell carcinoma metastases. Am J Surg 2011;202:158–67.
[9] Treasure T. Pulmonary metastasectomy: a common practice based on a weak evidence. Ann R Coll Surg Engl 2007;89:744–8.
[10] Van Reamdonck D, Friedel G. The European Society of Thoracic Surgeons Lung Metastasectomy Project. J Thorac Oncol 2010;5:S127–9.
[11] Fourquier P, Regnard JF, Rea S, Levi JF, Levasseur P. Lung metastases of renal cell carcinoma: results of surgical resection. Eur J Cardiothorac Surg 1997;11:17–21.
[12] Pogrebniak HW, Haas G, Linehan WM, Rosenberg SA, Passi HI. Renal cell carcinoma: Resection of solitary and multiple metastases. Ann Thorac Surg 1992;54:33–8.
[13] Morrow CE, Vassilopoulos PP, Grage TB. Surgical resection for metastatic neoplasms of the lung: experience at the University of Minnesota Hospitals. Cancer 1980;45:2981–5.
[14] Jett J, Hollinger CG, Zinsmeister AR, Pairorelo PC. Pulmonary resection of metastatic renal cell carcinoma. Chest 1983;84:442–5.
[15] Cerfolio RJ, Allen MS, Deschamps C, Daily RC, Wallrichs SL, Trastek VF *et al.* Pulmonary resection of metastatic renal cell carcinoma. Ann Thorac Surg 1994;57:339–44.
[16] Hofmann HS, Neef H, Krohe K, Andreev P, Silber RE. Prognostic factors and survival after pulmonary resection of metastatic renal cell carcinoma. Eur Urol 2005;48:77–81, discussion 81–2.
[17] Oddsson SJ, Hardarson S, Petursdottir V, Jonsson E, Sigurdsson MI, Einarsson GV *et al.* Synchronous pulmonary metastases from renal cell carcinoma – a whole nation study on prevalence and potential resectability. Scand J Surg 2012;101:160–5.
[18] Aberg T, Malmberg KA, Nilsson B, Nöu E. The effect of metastasectomy: fact or fiction? Ann Thorac Surg 1980;30:378–84.