Role of RPLND and Metastasectomy in the Management of Oligometastatic Renal Cell Carcinoma

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Abstract

Although lymphadenectomy is currently accepted as most accurate and reliable staging procedure for lymph node metastases, its therapeutic benefit in renal cell carcinoma (RCC) still remains controversial. Although the new, targeted therapy paradigms have changed the treatment of patients with advanced RCC and offer prolonged survival, cure is extremely uncommon in the absence of surgical resections. In this paper, the current role of metastasectomy is reviewed. Review the available literature concerning the role of retroperitoneal lymph node dissection and metastasectomy in outcome of oligometastatic RCC. A PubMed search was conducted to identify original articles, review articles, and editorials addressing the role of retroperitoneal lymph node dissection and metastasectomy in outcome of oligometastatic RCC. Keywords included renal tumors, renal cell cancer, kidney cancer, lymphadenectomy, metastasectomy, and oligometastases. While there is no randomized study available, recent large observational studies have better defined the prognosis of patients with metastatic RCC with or without metastasectomy and RPLND. To date, the available evidence suggests that RPLND and metastasectomy may be beneficial when technically feasible in patients with locally advanced (unfavorable clinical and pathologic characteristics) and oligometastatic disease. A proportion of patients will achieve long-term survival with aggressive surgical resection.

Keywords Renal tumors · Renal cell cancer · Kidney cancer · Lymphadenectomy · Metastasectomy · Oligometastases

In 1995, Hellman and Weichselbaum proposed the existence of oligometastases; a clinical disease state when tumor early in the evolution of metastatic progression produce metastases which are limited in number and locations. The concept oligometastatic disease broadly includes synchronous disease, oligoprogressive disease, and metachronous disease or recurrent oligometastasis [1, 2].

Paget hypothesized in his seed and soil theory that metastases depends on interactions between tumor cell and target organ. RCC metastasize most commonly to the lymph nodes, lungs, bone, and liver owing to a complex interaction between the host, tumor microenvironment, and genetic instability of the tumor cells [3]. There are several factors which will influence the outcome of treatment. The most favorable prognostic factors we are aware of are DFI of longer than 12 months, solitary metastasis, curative resection, male sex, and sites of

metastasis (glandular organs—thyroid, salivary, adrenal, and ovary).

RCC represents 2–3% of all cancers, with highest incidence in western countries. Over the last two decades until recently, the incidence of RCC increased by about 2% worldwide [4]. Twenty-five to thirty percent of patients will have metastases at the time of diagnosis, and one third of patients develop metastases subsequently [5]. These patients will have poor prognosis but patients with solitary/oligometastatic disease amenable to resection will have better prognosis. The advanced current era of imaging has helped in increased identification of such oligometastatic disease state, which is potentially amenable to surgery with the aim of achieving long-term survival. There are different modalities to treat such patients.

In a recent publication, the distribution according to different organs was 45.2% in the lungs, 29.5% in the bone, 21.8% in lymph nodes, and 20.3% in the liver. It was observed that in patients with multiple metastatic sites, 16% were in the brain and 49% in the bone, respectively [6]. The first pulmonary metastasectomy was reported in 1938 by Barney and Churchill with patient survival of more than 20 years after surgery without any evidence of recurrence [7]. In the series

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of Piltz et al., the 5-year overall survival of 105 patients of curative resection of lung metastases was 40%. They have also found significant dependent prognostic factors, i.e., complete resection, metastatic size less than 4 cm diameter, and tumor-free lymph nodes at the time of primary surgery [8].

In these three studies (Table 1), the OS rates were consistently around 40% in R0 resection, which is significantly higher than 3–11% survival reported for patients who did not undergo metastasectomy [8, 10, 11]. Factors impart longer survival post-operatively were fewer in pulmonary metastases, lack of lymph node involvement, pathological evidence of complete resection, and longer DFI [9].

The bone is the second most common site for renal cell carcinoma metastases, i.e., around 20–25% at initial presentation and is associated with poor prognosis with a median survival of 12 months [12]. Several studies have evaluated the role of resection of osseous metastases in renal cell carcinoma. The most common sites of surgical treatments were the spine, femur, pelvis, and humerus. The survival was better in patients with solitary metastases, wide resection, and absent axial skeletal involvement. In the series of Jung et al., 8 of 99 patients who had wide resection of solitary osseous metastases in combination with a nephrectomy had DSS rate of 100%. Five-year overall survival was 32.5%. Patients who underwent wide excision had low recurrence rate as compared to the intralesional procedures [13].

Solitary liver metastases of renal cell carcinoma occur only in 2–4% of cases [14]. Patients presenting with liver metastases at initial presentation will have poor prognosis than other sites of metastases. The median survival of liver metastases cases without treatment was 7.8 months [15]. However, in the series of Ruys et al., the 5-year survival of 33 treated patients with liver metastases was 43% in selected patients than 10% in the whole group [16]. Ruy et al. noted in their series that patients treated for liver metastases had 5-year survival of 43% as compared to 10% otherwise. In older series of liver resection, mortality was up to 30% but because of the advanced surgical techniques in liver resection and intensive post-operative care, the mortality due to procedure is reduced to 0–2% and

morbidity to 20.1% [1]. Corroborating another study primarily evaluating patients with low-grade (grades 1 and 2) primary RCC and ECOG of 0 was found to be independently and strongly associated with improved median survival. McKay et al's series, patients with multiple metastatic sites, median OS was 23.5 months in those without BM and LM and was worse in patients with the presence of either BM (16.1 months) or LM (18.2 months). The combination of both BM and LM had the shortest median OS (10.9 months). These studies suggest that metastasectomy may have a role for carefully selected patients particularly those with metachronous metastases, low-dose disease burden, and favorable location for resection. High-grade RCC as well as patients with synchronous metastases did not get much benefit from surgery [17].

RCC metastasizes rarely to pancreas in metachronous fashion. In autopsy series of primary RCC, pancreatic metastases were noted in 1.3–1.9% [18]. Pancreatic metastasis is often the only metastatic lesion with good prognosis and is rarely symptomatic. In CT scan, imaging lesion appears as hyper vascular lesions. RCC metastases to pancreas following long-term DFI, and the appearance of metastatic disease many years after nephrectomy is a well-known feature of RCC and is associated with more favorable outcome than early recurrence [19]. In a recent study done by Yuasa and colleagues, data was evaluated from 20 patients who underwent pancreatic metastasectomy between 1999 and 2013. Synchronous pancreatic metastases were found in three patients at the time of diagnosis. The median duration from diagnosis of RCC to pancreatic metastasis was 7.8 years, estimated median recurrence-free survival was 1.8 years. The perioperative morbidity rate was 16% with no mortality [20].

In a recent population-based analysis, lung metastasis was most frequent at 45.2%, followed by the bone at 29.5%, the lymph nodes at 21.8%, and the liver at 20.3% [21]. It was found that the proportion of patients with multiple metastatic sites was higher in young patients, 16 and 49% of which had brain and bone metastases, respectively. Adrenal metastasis has been found in 3.1–5.7% in nephrectomy series. In 347 patients with advanced stage disease (T3-4N0-1M0-1),

Table 1 Results of pulmonary resection of metastatic renal cell carcinoma

Study year	Study period	Total number of patients	5-year OS	Prognostic factors	Ref
Piltz et al. 2002	1980–2000	105 (150 surgical procedures)	40%	Complete resection Less than 4 cm diameter of metastasis Tumor-free lymph node	[8]
Pfannschmidt et al. 2002	1985–1999	191 (145 males, 46 females) 149 complete resection	36.9% (R0–41%, R1–22%)	Less than five pulmonary metastases DFI of more than 23 months Absence of mediastinal lymph node involvement	[10]
Cerfolio et al. 1994	1965–1989	96 (64 males, 32females)	35.9%	Solitary metastases DFI of more than 3.4 years	[11]

adrenal metastases occurred in 8.1% [22]. Presence of distant metastases, vascular invasion within the primary tumor, and multifocal growth of renal cell cancer within the tumor-bearing kidney were identified as independent predictors of adrenal metastases [23]. Isolated, synchronous contralateral, and metachronous ipsilateral or contralateral adrenal metastases are rare. Patients after surgical resection had an improved 5-year survival rate of 51% compared to 18% treated with systemic therapy and 13% with observation alone. Contralateral adrenal involvement, either synchronous or metachronous, is rare. In one autopsy series of patients after nephrectomy for RCC, it was observed in 0.7% [24].

First reported radical nephrectomy was performed by Mortensen in 1948 [25] (Fig. 1). The extended LND for RCC was first proposed by Robson CJ in 1969, which included all paraaortic and paracaval lymph nodes from crus of the diaphragm to the bifurcation of aorta. He reported positive lymph nodes of about 22.7% with improved 5-year survival advantage of 35% [27]. Recently, the new boundaries of LND have been described depending upon the side of the tumor. Parker has demonstrated that the primary regional drainage of kidney is predictable. On the right side, the regional nodal drainage is to the paracaval, pre-caval, post-caval, and interaortocaval nodes. On the left side, paraaortic, pre-aortic, post-aortic, and interaortocaval nodes. However, secondary drainage is variable and unpredictable [28]. In the study done by Herrlinger et al., they have compared extended lymph node dissection (320 patients) with only facultative LND (191 patients). They found positive lymph nodes in 17.5% with extended LND and 10% in facultative LND. Five- and 10-year survival rates were 58 and 40.9% in facultative LND and 66 and 56% in extended LND, respectively [29]. In the study

Table 2 Intraoperative nomogram for triggering a lymph node dissection [32]

Feature	Odds ratio (95% CI)	<i>p</i> value
Nuclear grade:		
1 + 2	1.0 (reference)	
3 + 4	5.25 (1.99–13.82)	< 0.001
Sarcomatoid component	4.11 (2.08–8.12)	< 0.001
Tumor 10 cm or greater	2.17 (1.27–3.70)	0.005
Primary tumor stage:		
pT1 + pT2	1.0 (reference)	
pT3 + pT4	2.00 (1.13–3.55)	0.017
Histological tumor necrosis	1.86 (1.00–3.48)	0.051

done by Whitson et al., 9586 patients with RCC who underwent radical or partial nephrectomy with lymphadenectomy were included. They have found out patients with positive lymph nodes had increased DSS with extent of lymphadenectomy. An increase of 10 lymph nodes in patient with 1 positive lymph node as associated with 10% absolute increase in DSS at 5 years; however, patients with negative lymph nodes had no effect on DSS with increase in extent of LND [30]. In a study done by Delacroix et al., 68 patients had pathological regional node-positive disease out of 2521 patients and noted to have 5-year OS and DSS of 37 and 39%, respectively, in patients who underwent nephrectomy and LND. In this study, predictors of favorable outcome were ECOG performance status of 0, single node involvement, absence of sarcomatoid features, and papillary histology. Patients with single-positive lymph node had a significantly prolonged TTR (37.2 months) [31]. In a recent analysis, it was

Fig. 1 Location of +LN based on the side of primary tumor [26]

demonstrated that the presence of nuclear grade 3 or 4, sarcomatoid component, tumor size > 10 cm, tumor stage pT3 or pT4, and presence of coagulative tumor necrosis were independent predictors of regional LN involvement at the time of nephrectomy. LN involvement increases as the number of risk factor increases, varying from 0.4–50% [32].

Terrone et al. in their study found that the rate of finding a positive node significantly increased from 10.2 to 20.8% with removal of ≥ 13 LNs when compared with removal of < 13 LN, and the authors also analyzed that tumor will be inadequately staged when limited LND (< 12 LNs) is done [33] Table 2. In 2008, the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary group conducted a randomized study which showed no survival advantage for clinically node-negative patients treated with nephrectomy alone compared with nephrectomy and LND. The limitation of the study was that, most of the patients had low-stage tumors with a negligible risk for nodal involvement [34].

Conclusion To date, the available evidence suggests that RPLND and metastasectomy may be beneficial when technically feasible in patients with locally advanced (unfavorable clinical and pathologic characteristics) and oligometastatic disease. A proportion of patients will achieve long-term survival with aggressive surgical resection.

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