A systematic review of the role of hepatectomy in the management of metastatic renal cell carcinoma

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Abstract

Aim: This review sought to systematically appraise the literature to establish the role of hepatectomy in treating renal cell carcinoma hepatic metastases.

Method: Medline and EMBASE were systematically searched for papers reporting survival of patients who underwent hepatectomy for metastatic renal cell carcinoma.

Results: Six studies containing 140 patients were included. There were no randomised controlled trials. Perioperative mortality was 4.3%, with reported morbidity between 13 and 30%. Patients with metachronous presentation, and a greater time interval between resection of primary tumour and development of metachronous metastases, appeared to have better survival. There was no difference in survival between patients with solitary and multiple metastases.

Conclusion: Few patients with hepatic metastases from renal cell carcinoma are suitable for hepatectomy as metastatic disease is usually widespread. Selected patients may experience a survival benefit, but identifying these patients remains difficult.

Keywords: Renal cell carcinoma; Metastatic renal cell carcinoma; Hepatectomy

Introduction

While hepatectomy has been shown to provide a survival benefit in the treatment of metastatic disease from a variety of malignancies, 1,2 its role in the treatment of metastatic renal cell carcinoma is not clear. Renal cancer is the tenth commonest cancer worldwide and accounts for approximately 2% of all cancers diagnosed. 3 It is more common in developed countries and the incidence is rising. 3 Renal cell carcinoma accounts for approximately 90% of all renal malignancies. 3 At time of diagnosis, 25–30% of patients will have metastatic disease 5 and of those with localised disease, a further third will develop metastases after resection of the primary tumour. 6

Treatment options for metastatic renal cancer are limited, with the British Association of Urological Surgeons guidelines recognising that there is currently no consensus on the optimal treatment strategy. 7 Renal cell carcinoma is generally resistant to chemotherapy. 8 There are a number of newer agents including immunotherapy agents and angiogenesis inhibitors which may have a role in the treatment of metastatic disease 7 although these agents generally have a low response rate. 9 The limited treatment options mean that prognosis in metastatic renal cell carcinoma is poor, with 5-year survival typically less than 10%. 10 The lungs are the commonest site of metastatic spread, accounting for 75% of cases of metastatic disease. 11

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that resection of pulmonary metastases provides a survival benefit\textsuperscript{12–14} and consideration of pulmonary resection for limited lung disease is currently recommended in British Association of Urological Surgeons guidelines. Guidelines issued by the European Association of Urology in 2014 concluded that “retrospective comparative studies consistently point towards a benefit of complete metastasectomy in metastatic renal cell carcinoma patients in terms of overall survival, cancer-specific survival and delay of systemic therapy” however they then stated that no general recommendations could be made due to the sparsity of strong evidence and that the decision to resect metastatic disease should be made on a case-by-case basis.\textsuperscript{15}

The liver is involved in 20–40% of cases of metastatic renal cancer\textsuperscript{11,16} usually as part of widespread dissemination. However, in 2–4% cases metastases are liver limited, and therefore may be amenable to surgical resection.\textsuperscript{17} The evidence base supporting hepatectomy for metastatic renal cell carcinoma is limited. This study therefore sought to systematically evaluate the literature to offer guidance on the role of hepatectomy in patients with metastatic renal cell carcinoma.

Methods

Medline and EMBASE databases were searched on 01/07/13 and all reference from 1993 to this date were potentially eligible for inclusion. Searched terms used were “cancer OR malignant OR malignancy OR neoplasm OR neoplastic”, “liver OR hepatic”, “metastatic OR metastasis OR metastases OR secondary OR secondaries”, “surgery OR resection OR hepatectomy OR hepatectomy OR segmentectomy OR segmentectomies OR metastasectomy OR metastasectomies” and “kidney OR renal”.

Title search was conducted by a single author of all identified references, with those not relating to metastatic renal cell carcinoma excluded. Of the remaining references, abstracts were retrieved and independently assessed by two authors against inclusion/exclusion criteria. Of those abstracts considered eligible, full papers were obtained and underwent review by two authors independently against inclusion/exclusion criteria. Where discrepancies arose between two authors regarding inclusion, discussion between the authors was used to reach a consensus.

Inclusion criteria

- Paper presenting data on resected liver metastases from renal cell carcinoma
- Original data published (e.g. not review papers)
- Survival outcome available

Exclusion criteria

- Non-English language studies
- Full manuscript not available (e.g. abstracts presented at conference)

- Studies with less than ten patients
- Malignancy other than renal cell carcinoma
- Multiple papers published from same patient data set

Primary outcome was survival following hepatectomy; secondary outcomes included morbidity and mortality data and factors considered to be prognostic for survival, e.g. presentation of metastases (synchronous versus metachronous) or extent of metastases (solitary versus multiple metastases).

Results

The database searches returned 1729 citations. Fig. 1 shows how many of these were included/excluded at each stage of the search process. After inclusion and exclusion criteria were applied to identified abstracts, nine studies remained. Full papers of these were obtained. Two papers\textsuperscript{11,18} contained data on the same series of patients. Alves et al.\textsuperscript{18} was published in 2003 and included 14 patients with metastatic renal tumours (10 of which were renal cell carcinoma). Aloia et al.\textsuperscript{11} was published in 2006 included 19 patients, 16 of whom had renal cell carcinoma. Despite Aloia et al.\textsuperscript{11} being more recent and containing more patients, this was excluded as data on patients with renal cell carcinoma and patients whose tumours were of embryonal origin were included together in outcome data, which may have skewed results. Alves et al.\textsuperscript{18} presented data for each of the fourteen patients individually, allowing data on only those patients with metastatic renal cell to be extracted and included in this review and so was included, despite being older and including fewer patients. Two further papers were excluded as they did not contain sufficient data; one reported on only two patients with hepatic metastases\textsuperscript{19} and the other did not contain specific survival data on hepatic metastases of renal cell carcinoma origin.\textsuperscript{20}

Six studies\textsuperscript{18,21–25} met the criteria for inclusion in this review and are summarised in Table 1. There were no randomised controlled trials. Two studies\textsuperscript{22,25} presented data which were retrospectively collected from a prospectively maintained database, three studies\textsuperscript{18,21,23} presented data which were retrospectively collected and one study\textsuperscript{24} did not state the method of data collection.

Figure 1. Diagram showing how many citations were included/excluded at each stage.
Alves et al. published a series of fourteen patients with renal tumours, only ten of which were renal cell carcinoma. Data were only extracted and included in this review for these ten patients. Ruys et al. published a series of thirty-three patients, four of whom underwent radiofrequency ablation as their sole method of management for hepatic metastases. Data on these four patients were included with the survival outcome data of the remaining twenty-nine who underwent hepatectomy. Data from patients treated by radiofrequency ablation may skew the results as morbidity and mortality is likely to be lower for this less invasive procedure for smaller disease burden.

Patient demographics

The six studies included data on a total of 140 patients. The majority of patients were male (male-to-female ratio 1.6:1) and median age ranged from 47 to 62 years old. In metachronous disease, median interval from resection of primary tumour to diagnosis of metachronous disease ranged from 17 to 55 months; some cases presented later than ten years after primary resection.

Neoadjuvant and adjuvant therapy

Three studies reported the use of neoadjuvant and adjuvant therapy. Minimal data were published on exact agents prescribed. Timing of these was reported in two papers; nine patients received neoadjuvant therapy and twenty-nine patients received adjuvant therapy. Ruys et al. did not report how many patients had either neoadjuvant or adjuvant therapy. No comparisons were possible between those treated with chemotherapy plus resection or resection alone.

Hepatectomy criteria

Indications for hepatectomy were poorly defined. Three studies did not report the criteria by which they decided if patients were potential candidates for surgery. Two studies considered hepatectomy “if it were likely to be curative and if there was no irresectable extrahepatic disease” while the final study simply stated that extrahepatic metastases were not a contraindication to surgery if this was technically amenable to resection.

Surgical resection

All studies included data on surgical procedures performed. There were ninety-two major hepatectomies and forty-three minor hepatectomies. These are further detailed in Table 2. Only one study reported the total number of patients identified as having hepatic metastases from renal cell carcinoma, with Langan et al. reporting that 4% of patients identified proceeding to hepatectomy.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Journal</th>
<th>Year</th>
<th>Patients</th>
<th>Median age (range)</th>
<th>Male/female</th>
<th>Period included</th>
<th>Resection criteria</th>
<th>Disease burden</th>
</tr>
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<tbody>
<tr>
<td>Alves et al.</td>
<td>Annals of surgical oncology</td>
<td>2003</td>
<td>10</td>
<td>55 (30–76)</td>
<td>6/4</td>
<td>82-01</td>
<td>Resection likely to be curative; absence of irresectable extrahepatic metastases</td>
<td>2 synchronous/8 metachronous 3 solitary/7 multiple 8 unilobar/2 bilobar 9 synchronous/34 metachronous 24 solitary/19 multiple 37 unilobar/6 bilobar 5 synchronous/5 metachronous 7 solitary/3 multiple 10 unilobar 10 synchronous/23 metachronous 19 solitary/14 multiple 30 unilobar/2 bilobar 17 metachronous</td>
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<td>HPB</td>
<td>2012</td>
<td>43</td>
<td>62b</td>
<td>29/14</td>
<td>94-11</td>
<td>Not listed</td>
<td>9 synchronous/34 metachronous 24 solitary/19 multiple 37 unilobar/6 bilobar 5 synchronous/5 metachronous 7 solitary/3 multiple 10 unilobar 10 synchronous/23 metachronous 19 solitary/14 multiple 30 unilobar/2 bilobar</td>
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<td>Langan et al.</td>
<td>Journal of cancer</td>
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<td>10</td>
<td>47 (32–58)</td>
<td>8/2</td>
<td>80-10</td>
<td>Resectable Extrahepatic disease was not a contraindication to resection</td>
<td>5 synchronous/5 metachronous 7 solitary/3 multiple 10 unilobar 10 synchronous/23 metachronous 19 solitary/14 multiple 30 unilobar/2 bilobar 17 metachronous</td>
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<tr>
<td>Stief et al.</td>
<td>The journal of urology</td>
<td>1997</td>
<td>13</td>
<td></td>
<td></td>
<td>83-93</td>
<td>Not Listed</td>
<td>30 synchronous/34 metachronous 37 unilobar/6 bilobar 5 synchronous/5 metachronous 7 solitary/3 multiple 10 unilobar 10 synchronous/23 metachronous 19 solitary/14 multiple 30 unilobar/2 bilobar</td>
</tr>
<tr>
<td>Thelan et al.</td>
<td>World journal of surgery</td>
<td>2007</td>
<td>31</td>
<td>58 (28–70)</td>
<td>19/12</td>
<td>88-06</td>
<td>Resection likely to be curative in absence of irresectable extrahepatic metastases</td>
<td>6 synchronous/25 metachronous 25 unilobar/6 bilobar</td>
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</tbody>
</table>

a 1 patient had ablation only.
b Mean age.
c 4 patients had radiofrequency ablation only.
d Data on unilobar vs bilobar disease pattern only provided for 32 out of three 33 patients.
Mortality and morbidity rates were reported in a variety of ways; “60-day mortality”, “30-day mortality” and simply “post-operative mortality”. Six deaths were reported across the six included studies, corresponding to a mortality rate of 4.3%. This was heavily skewed by Stief et al. who reported a mortality rate of 31% (four deaths from 13 hepatectomies).24 Morbidity was only reported in four studies, and in these morbidity rate ranged from 12.9 to 30%.21 The time frame within which complications occurred were not published in any of the papers. Table 2 details the morbidity reported in each study.

Survival outcomes were reported as 1-, 3- and 5-year survival rates and median survival. Four studies reported 1-year survival as 78–94.2%, 3-year survival as 45–62.1%.21–23,25 and three studies reported 5-year survival as 34–43%.22,23,25 Median survival ranged from 16 to 48 months.22–25 Table 3 summarises survival outcomes.

Several prognostic factors were identified. Three studies compared survival of patients with solitary and multiple metastases.21–23 None of these studies demonstrated a difference in survival. Three studies compared survival in patients with synchronous presentation with patients with metachronous presentation, two of which demonstrated a statistically significant difference.22,23,25 Langan et al. reported median survival of 13 and 68 months (p = 0.02) for patients with synchronous and metachronous metastases respectively.22 Ruys et al. reported median survival of 18 and >37 months (p = 0.03) for patients with synchronous and metachronous metastases.23 Five studies investigated the disease-free interval (DFI), i.e. time from resection of primary tumour to diagnosis of metastatic disease.18,21–23,25 Hatzaras et al. demonstrated a difference in median survival between DFI <12 months and >12 months of 21.5 months and median survival not reached by end of study period (p = 0.022) and Thelan et al.25 demonstrated a difference in median survival of 18 months and 79 months for patients with DFI <24 months and >24 months respectively.

Discussion

Hepatectomy is seldom used in the treatment of metastatic renal cell carcinoma, but for selected patients may offer a reasonable option for control of metastatic disease. Phylo- genetic exome sequencing suggests that renal cell cancer progresses to a widespread metastatic phenotype from multiple tumour subclones within a primary lesion. Metastases can therefore give rise to further subclones of metastases26 providing a biological rationale for resection of limited oligometastatic disease.
It has been shown that hepatectomy can be performed safely with a mortality rate of <1%.\(^2\)\(^7\) Mortality after resection for RCC was higher in this series, but was skewed by a historical series reporting resections performed in the late 1970’s.\(^2\)\(^4\) The safety of resectional liver surgery has improved markedly over this period, with more recent series reported an overall mortality of 1.6%.

Despite the potential survival benefit of hepatectomy, few patients are suitable candidates for resection. Of the six papers included in this review, only one paper provided data on proportion of patients progressing to resection. Langan et al. reported a 4% resection rate,\(^2\)\(^2\) which is in keeping with the literature describing limited, localised metastatic disease in only 2–4% patients.\(^1\)\(^7\) This is a highly selected cohort of patients with very few meeting criteria for resection. Unfortunately, criteria for resection was poorly reported in the studies included, with three not reported any information on their selection criteria at all.\(^2\)\(^1\),\(^2\)\(^3\),\(^2\)\(^5\) As such, this review is unable to offer guidance as to which patients may be considered candidates for resection.

Three studies reported 5-year survival rates of greater than 30%\(^2\)\(^2\),\(^2\)\(^3\),\(^2\)\(^5\) which is significantly better than that achieved with palliative chemotherapy. Although it can be argued that this survival benefit has been achieved through selection, the limited number of patients presenting with liver limited disease would make future prospective comparison impossible.

Interestingly, Hatzaras et al. published data patients who had undergone hepatectomy for colorectal cancer as a comparison cohort.\(^2\)\(^1\) There was no statistically significant difference in 1-year, 3-year or median survival when those with resected renal cell carcinoma metastases compared with those with resected colorectal metastases. If similar outcomes can be achieved for resection of renal cell carcinoma hepatic metastases as have been seen in colorectal metastases, this could be a viable treatment modality for a disease with limited treatment options at present.

As only highly selected patients would be potential candidates for hepatectomy, several potential prognostic factors were investigated to help determine which groups of patients would benefit most from resection. Poorer survival was not found to be associated with multiple hepatic metastases.\(^2\)\(^1\)\(^,\)\(^2\)\(^3\)\(^,\)\(^2\)\(^5\) Timing of detection of metastases was a prognostic indicator in two ways. Firstly, two studies demonstrated that those with metachronous presentation of metastases had a favourable outcome following hepatectomy compared to patients with synchronous presentation.\(^2\)\(^2\),\(^2\)\(^3\) Secondly, three studies demonstrated longer survival was associated with greater disease free interval.\(^1\)\(^,\)\(^8\),\(^2\)\(^1\),\(^2\)\(^5\) Similar patterns have been

<table>
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<th>Paper</th>
<th>Patients</th>
<th>Survival 1 year</th>
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<th>Survival 3 years</th>
<th>Survival 5 years</th>
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<td>Alves et al.(^1)(^8)</td>
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<td>47%</td>
<td>43%</td>
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<td>Overall 13</td>
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<td>54.3%</td>
<td>38.9%</td>
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<td>DFI &gt;24 79</td>
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DFI: disease free interval.
NR: not reached.
\(^a\) Mean survival (months).
demonstrated in other settings. It has been shown that following hepatectomy for colorectal metastases, patients whose disease recurs early tend to have a worse prognosis than those whose disease recurs at a later stage.28,29 This may be a reflection of less favourable biology, as it was shown that patients with early recurrence were more likely to have had multiple tumours resected compared to those who develop recurrence at a later stage, possibly reflected a more aggressive tumour.29

This study was limited by the quality of the evidence base. This probably reflects the limited role hepatectomy has within this patient group. Survival outcomes were better than patients treated with palliative intent, but direct comparison was not possible. Patients were highly selected with limited disease, and as such would be expected to have better prognosis than patients with metastatic renal cell carcinoma in general. The exact benefit of resection in this group of patients cannot be determined without a randomised controlled trial. Three of the studies had less than fifteen patients included in their series.18,22,24 This highlights the difficulty in generating high quality evidence in this area; the number of patients with liver limited disease that may be considered for hepatectomy are so few that recruiting sufficient number of participants for a randomised controlled trial would be extremely difficult.

The evidence supporting hepatectomy for the management of metastatic renal cell carcinoma is weak, and as such, firm conclusions cannot be drawn from this review. There were no randomised controlled trials and included studies were small. Patients who present with limited hepatic metastatous metastases with significant disease free interval, or established favourable tumour biology following primary tumour resection may benefit from hepatectomy however the exact benefit is not known and patient selection remains difficult. This is in keeping with a recent paper by Page et al.30 which reviewed the literature for studies reporting on the indication of surgical resection of hepatic metastases from a non-colorectal, non-neuroendocrine origin. The paper reviewed a number of primary malignancies, including renal cell carcinoma. No well defined indications for hepatectomy were identified for these metastases, but noted that selected patients may be suitable candidates for surgical resection.30 Selected patients may experience a survival benefit, following hepatectomy for renal cell liver metastases, however identifying these patients remains difficult. A randomised controlled trial would be challenging to deliver; a prospective collaborative registry for patient undergoing hepatectomy for renal cell carcinoma metastases may help improve identification of patients in whom hepatectomy offers benefit.

Conflict of interest statement

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References


