Gallbladder’s clear cell renal cell carcinoma metastasis: A systematic review of the literature

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Renal cell carcinoma (RCC) represents 2% of all cancers, being the clear cell subtype the most common among renal tumors (70-80%). RCC is well known for its capacity to metastasize in an early stage of the disease, gallbladder metastases are considered extremely rare. The symptomatology goes from asymptomatic to cholecystitis like-symptoms. Ultrasonography, may be often, the first diagnostic tool, tumors can appear under different hyperechoic masses without acoustic shadowing. Metastasectomy has gained a wide consensus because of the possibility of extending survival, keeping in mind the importance of selection of the ideal candidate for it. The surgical procedure will be chosen upon the extend of the disease, it may go from a simple cholecystectomy to a cholecystectomy associated with a wedge/right hepatic lobectomy for curative purposes. We performed a systematic review of 77 cases of gallbladder’s clear cell renal cell carcinoma metastasis published from 1963 up to date, analyzing the symptomatology at presentation, diagnosis, treatment, prognosis, and surgical procedures.

Keywords: Clear cell renal cell carcinoma; metastatic renal cell carcinoma; gallbladder; diagnosis; therapy


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Introduction

Renal cell carcinoma accounts for 2% of all cancers. Renal Renal cell carcinoma (RCC) originates in the renal cortex and and clear cell carcinoma is the most common form of renal tumor and accounts for 70-80% of all cases of RCC [1-2]. RCC RCC is well known for its capacity to metastasize in an early stage of the disease. In decreasing order of frequency, the lung, bone, liver, nodes, skin and brain are the most common sites of metastasis from clear cell renal cell carcinoma (ccRCC). Some metastases can be easily inspected, such as those affecting the genitalia, breast, or parotid gland, or those that most easily give rise to clinical symptoms, such as bleeding and obstruction, as in the case of the ureter, bladder, intestine, and pancreas. On the other hand, metastases involving the viscera, such as the serosa, gallbladder, spleen, and endocrine glands, are rarely or never discovered [3]. Gallbladder metastasis from ccRCC are extremely rare, in a large autopsy series, the gallbladder was site of metastasis in only 4 of 687 (0.6%) cases of RCC [4].
<table>
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<tr>
<th>Age</th>
<th>Gender</th>
<th>Interval from</th>
<th>Mode</th>
<th>Involvement of</th>
<th>Signs and symptoms</th>
<th>Surgery</th>
<th>Macroscopic</th>
<th>Size</th>
<th>Stones</th>
<th>Follow-up</th>
<th>Outcome</th>
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<td>AWD</td>
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<td>No</td>
<td>2 yr</td>
<td>DOD</td>
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<td>Gekiya et al 2002</td>
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<td>No</td>
<td>1 yr</td>
<td>NED</td>
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<td>Aoki et al 2002</td>
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<td>Meta/27 yr</td>
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<td>No</td>
<td>6 yr</td>
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<td>Miyagi et al 2003</td>
<td>53 M</td>
<td>Meta/10 yr 6 mo</td>
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<td>NA</td>
<td>LC</td>
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<td>25x15</td>
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<td>Scalp</td>
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<td>Mass</td>
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<td>Park et al 2003</td>
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<td>NA</td>
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<td>NA</td>
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Table 1. Reported cases of metastatic renal cell carcinoma of the gallbladder
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<th>Authors</th>
<th>Gender</th>
<th>Age</th>
<th>Stage</th>
<th>Tissue</th>
<th>Symptoms</th>
<th>TNM</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Histology</th>
<th>Location</th>
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<td>52</td>
<td>N/A</td>
<td>Pancreas</td>
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<td>Pedunculated</td>
<td>25x25</td>
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<td>1 yr 10 mo NED</td>
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<td>M</td>
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<td>LC</td>
<td>Pedunculated</td>
<td>30x20</td>
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<tr>
<td>Ichikawa et al. 2011</td>
<td>M</td>
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<td>Chung et al. 2012</td>
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<td>SC</td>
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<td>35x20</td>
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<td>7 yr AWD</td>
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A systematic search of the literature was performed to identify all relevant articles regarding gallbladder’s clear cell renal cell carcinoma metastasis. A research in the National Library Of Medicine (PubMed; 1960 to present), SCOPUS, ScopeMed, Cochrane Library, Embase, and Google Scholar was made. Using the search terms “renal cancer”, “clear cell renal cell carcinoma”, “metastasis”, “gallbladder” and “metastatic renal cell carcinoma”. We also searched the reference lists of the articles that came out with our primary search. The abstracts of all identified articles were studied and selection was based on the relevance for the subject. We included all 66 articles, from which, 63 full-text articles and 3 abstracts. A total of 77 cases of gallbladder’s clear cell renal cell carcinoma metastasis were reported from 1963 up to date.

All articles were carefully analyzed for age of the patients, gender, lapse of time between primary tumor and metastasis...
presentation, metastasis to other organs, as well as, symptoms at presentation, surgical technique, macroscopic findings within the gallbladder, size of the gallbladder’s metastasis, concomitant presence of stones, follow-up period, and outcome (Table 1).

Results

Between 1963 and the beginning of 2016, sixty-six case reports on gallbladder’s clear cell renal cell carcinoma (ccRCC) metastasis have been reported, with a total of 77 patients (45 males, 21 females, 11 cases did not reported the sex of the patient), the mean age was 60.98 years old, with a median of 63 years old and a range of 45 (being 39 years old the youngest and 84 years old the oldest patient).

Out of the 77 cases, in 50 patients the metastatic disease to the gallbladder presented in a metachronous matter, whereas in 17 patients its presentation was synchronous. The mean lapse time from primary tumor to gallbladder’s metastasis was 7.4 years, ranging from 3 months to 27 years. In twenty-eight cases the gallbladder’s metastasis presented as a solitary metastasis, while in thirty-seven cases it presented in a scenario of multiple metastatic disease, being the lung the most frequent co-metastatic organ.

According with cases reported in literature, the majority of metachronous metastasis to the gallbladder from ccRCC did not present any symptomatic (21 cases), while ten patients had acute biliary symptoms at presentation, and the rest fluctuated from upper abdominal discomfort to hemobilia.

The surgical treatment for gallbladder’s metastasis from ccRCC according to the cases reported in literature was: simple cholecystectomy in 52 patients, from which 11 patients underwent laparoscopic cholecystectomy, whereas 11 patients underwent extended cholecystectomy (intended as a surgical procedure involving the removal of the gallbladder and nearby lymphadenopathy and/or liver tissue). In 11 cases the surgical procedure was not specify.

The shape of the gallbladder lesion was quality as polyloid in 39 of the reported cases (being the most frequent presentation), 16 cases were described as pedunculated, and 7 cases as a “mass” and the rest weren’t qualified. The concomitant presence of stones and metastatic lesion was reported in 17 patients, in contrast, 42 patients didn’t present stones. The mean follow-up time was 2.5 years, ranging from 1 month to 17 years of follow up.

In 23 patients there wasn’t any evidence of disease during the reported follow-up time, 12 patients were reported as alive with disease, 6 patients died of cancer, 3 patients died from other disease, and 33 patients didn’t have any report on the outcome.

Metastatic behavior of ccRCC

Metastatic spread to the gallbladder from intra- and extra-abdominal organs carcinomas has been reported previously, usually the metastatic lesion appears as an extraluminal mass due to peritoneal seeding or direct invasion. An intraluminal metastasis, is most likely hematogenous in origin, and has been reported from primary sites such as the skin, breast, lungs, esophagus, and kidney [15].

It is widely accepted that metastasis to the gallbladder from extra-abdominal organs are by way of the hematogenous embolic route [13-20], while intraperitoneal organs’ metastases emerge either by deposition on the serosa surface of the gallbladder, or by peritoneal implantation, or by direct invasion of the gallbladder [20]. Gallbladder metastases have been reported from other primary tumors, melanoma being the most frequent, followed by lung, esophagus, pancreas and colon carcinoma [26-36-42].

The metastatic pathway is not always predictable and certainly not for renal cancer, which is notorious for its complex lymphatic drainage. However there is a predilection for certain sites, meaning that these sites are usually the first occupied by cancer cells, for the RCC the lungs are the first metastatic target [65].

Metastases to the gallbladder often begin as a submucosal nodule that eventually becomes pedunculated and may resemble primary carcinoma of the gallbladder [28]. The metastatic carcinoma may be limited to the muscle layer and perimuscular connective tissue, and doesn't involve the mucosa, whereas primary tumors involve the mucosa [23].

The mean time from radical nephrectomy to metastasis has been reported to be 3.1 years. Rapid progression in patients who have no evidence of metastases at the time of presentation may occur due to aggressive tumor biology or subclinical metastases at the time of nephrectomy [66]. Even though there have been several reports of late metastases from RCC, even decades after potentially curative surgical excision of the primary tumor. There is evidence that distant metastatic disease will eventually develop in about one out of three patients with RCC, and in these cases the disease is considered incurable. There has been evidence in support of an early dissemination model, where metastases occur early in the lifecycle of cancer cells [65].
Diagnosis

The symptomatology varies from patient to patient, going from asymptomatic occasionally diagnosed during follow-up to cholecystitis-like symptoms. Ultrasonography (US) generally is the first diagnostic tool in galbladder tumors. Metastases can appear under different hyperechoic masses bigger than 1 cm in diameter, close to the gallbladder wall without posterior acoustic shadowing [49-67]. Color-Doppler is an important complementary technique since the detection of flow signals rules out biliary sludge and cholesterol polyps, and indicates an expansive lesion [42]. Primary tumors of the gallbladder often coexist with gallstones, while a polypoid lesion in an acalculous gallbladder is more consistent with a metastatic lesion rather than a primary tumor [20]. Another ecographic technique that has gained some consensus over the past years, is the contrast enhanced ultrasound (CEUS), that has shown to be helpful in the differential diagnosis between benign lesions and carcinomas of the gallbladder; carcinomas frequently present an intense and diffuse enhancement of the tumor vegetation. It appears that the early wash-out can be a key finding suggesting malignancy [67]. Destruction of the gallbladder wall intactness is absent in benign diseases, whereas it is present in the majority of carcinomas [68].

During Contrast-enhanced Computed Tomography (CT) a common appearance of the gallbladder carcinoma is either focal or diffuse gallbladder wall thickening [59]. A CT sign that helps to distinguish between primary gallbladder tumors and metastases, is the invasion of the mucosal layer. When the mucosa is not infiltrated, it indicates an invasion from the serosa layer, therefore the primary gallbladder tumor can be excluded. In tumoral gallbladder invasion by contiguous tumors, a big mass without clear limits may be observed [49]. Moreover, the majority of cases of metastatic renal cell carcinoma (mRCC) to the gallbladder reported in literature, presented themselves as polypoid lesions. Furukawa and Mizuguchi recommended that patients with hypervascular polypoid lesions in the lumen of the gallbladder (GB), who have a synchronous or a prior history of RCC should be considered as metastatic lesions regardless of the presence or absence of symptoms [54]. Hypervascularity, may be helpful in the differential diagnosis of a metastatic gallbladder tumor from RCC and a primary gallbladder carcinoma because the former is hypervascular [41].

Robledo et al., stated that it hasn't been proven any benefit from using positron emission tomography (PET) to detect gallbladder metastasis [49]. While Win asserts that FDG-PET is a good diagnostic tool in mRCC because it can detect cancers even before anatomic changes are perceptible [59].

In addition, mRCC should be differentiated from primary clear cell carcinoma of the gallbladder based on immunohistochemical examination. Clear cell carcinoma of the gallbladder is positive for CK7 and CEA, while mRCC is negative for these antigens [41]. Whereas, metastatic RCC of the gallbladder is positive for vimentin, but negative for CEA, CK7 and CK10 [29].

Currently, no clinically validated biomarkers are available to aid the early diagnosis, disease monitoring and treatment efficacy in ccRCC [69].

Treatment

Metastatic RCC presents a particular therapeutic challenge for clinicians because of the resistance of kidney cancer to chemotherapy or radiotherapy, and the limited response to immunotherapy. Therefore, surgical resection, when technically feasible, currently remains the only potentially curative treatment for RCC other than the rarely achieved durable complete responses to high-dose interleukin-2 [70].

Radical nephrectomy in the presence of metastatic disease (called debulking or cytoreductive nephrectomy) is often indicated before the start of systemic treatment in patients with metastatic disease as part of integrated management strategy. The exact mechanism that accounts for this beneficial effect is not known. Prevalent hypotheses are that cytoreductive nephrectomy (CRN) might remove a source of tumor-promoting growth factors or immunosuppressive cytokines. Alternatively, debulking nephrectomy might reduce the total burden of disease, thereby increasing the interval before the accumulation of a lethal tumor burden [71-72].

Two randomized, prospective trials were conducted in the United States (Southwest Oncology Group, SWOG) [73] and Europe (European Organization Research and Treatment of Cancer, EORTC) [74] under similar entry criteria to determine the effectiveness of CRN; by comparing CRN plus interferon alpha 2b vs. interferon alpha 2b alone. In the SWOG study, patients who underwent CRN and interferon α2b had a significantly improved median survival of 11.1 months compared to 8.1 months for the interferon α 2b alone group. The EORTC study, randomly assigned patients to receive interferon α2b alone or CRN plus interferon α2b. Time to disease progression (5 vs. 3 months) and median duration of survival (17 vs. 7 months) significantly favored the patients in the CRN/interferon α2b group [71]. The collective experience with chemotherapy in metastatic disease has shown very little benefit with a 5-6% overall objective response rate [72].
When there is a solitary metastasis, its surgical resection is indicated in selected patients, given the five-year survival rate of approximately 30%. However, patients who have solitary metastasis at the time of their initial diagnosis generally do poorly, even when the primary and metastatic sites are both resected aggressively [1].

Metastasectomy has gained a wide consensus because of the possibility of extending survival, even if it lacks a solid biological rationale to support it and has low levels of evidence and grade of recommendation. Furthermore, selection of the ideal candidate for metastasectomy is still poorly defined and is generally reserved for patients with a good performance status, and lesions that are technically resectable. In a prospective study by Antonelli et al., they found that the factors that had a significantly negative influence on RCC metastasectomy were the simultaneous presence of multiple metastases, and to a lesser extent, the synchronous diagnosis of metastasis compared with that of the primary tumor. In the cases where these two conditions were absent, the median estimated survival rate from metastasectomy was extremely satisfactory [75].

The extend of surgery depends on many factors such as the extend and spread of the tumor, and the age and general condition of the patients. For an early stage, an extended surgery with lymph node dissection of the porta hepatis and excision of adjacent liver tissue, ranging from a wedge resection to right hepatic lobectomy, rather than a simple cholecystectomy is preferred for a better prognosis [20].

Ishizawa et al., reported, in a case series, that no patients who underwent simple cholecystectomy have developed local recurrence in the liver or the bile duct, which may suggest that simple cholecystectomy would be sufficient for curative resection of metastatic RCC of the gallbladder. Furthermore, they discard the use of laparoscopy in patients preoperatively diagnosed as having metastatic cancers, because residual tumor and port-site or peritoneal recurrence after laparoscopic cholecystectomy have been reported in patients with primary gallbladder cancer [29]. Shoji et al., consider that a simple cholecystectomy may be sufficient for curative resection of gallbladder metastasis from RCC if there is no invasion of the muscle layer of the gallbladder in the pre-operative imaging and intra-operative findings [41]. Cholecystectomy with R0 resection has been proven to be the only factor that increases survival, mainly in isolated cases of metastasis. Acute cholecystitis as a clinical presentation is associated with poor prognosis. The five-year survival rate following cholecystectomy for mRCC is 35-50% [49].

On the other hand we have the targeted therapies, which are expected to interact with three different molecular pathways: the direct inhibition of VEGF and its receptor, the inhibition of the Raf/MEK/ERK pathway in the endothelial cells, and the inhibition of the PI3K/AKT/mTOR pathway in the tumor cells. Currently, seven drugs have the indication in mRCC: sunitinib, bevacizumab, axitinib, temsirolimus, and everolimus. Targeted therapies have the advantage of potentially downsizing and/or downstaging primary tumors, whereas prior surgery could delay the initiation of systemic treatments and induce morbidity. P. Bigot et al, underline the importance of surgery and its potential curative benefit of metastatic resection and particularly in case of solitary localizations. The OS (overall survival) of patients who underwent metastasectomy of a solitary lesion is about 35-60% at 5 years, but its benefit is highly dependent on the metastasis site. A Fuhrman grade's increase between the metastasis and the primary tumor has been reported to be pejorative in prognosis. In case of multiple RCC metastases, complete resection could also be associated with long-term survival. In a retrospective study including 877 patients who underwent nephrectomy and developed multiple metastatic tumors, a significant prolongation of cancer-specific survival was reported in those who underwent complete surgical resection. The 5-year CSS rate was 73.6% with complete resection versus 19% without complete resection (p <0.001). Currently two randomized prospective studies are recruiting, they were design to answer the following question: “Who are the best candidates for nephrectomy and what is the best timing in mCRR management?”, this studies are the SURTIME trial and the CARMENA trial. According to the European Association of Urology guidelines, nephrectomy combined with IFN-alpha is recommended to patients with mRCC who are suitable for surgery and have a good performance status (PS). In patients with synchronous metastatic spread, metastasectomy should be performed if the disease is resectable and if the patient has a PS. For the National Comprehensive Cancer Network guidelines, a cytoreductive nephrectomy is recommended before systemic therapy to patients with RCC who have potentially surgically resectable primary tumor and multiple metastases. The European Society Medical Oncology guidelines on Kidney cancer recommend, in routine practice, a cytoreductive nephrectomy to patients with good PS and large primary tumors, and also for patients with a symptomatic primary lesion. Cytoreductive nephrectomy is not recommended to patients with poor PS [76]. A Cochrane review on targeted therapy for advance renal cell cancer concluded that agents targeting VEGF and mTOR pathways improve PFS (progression-free survival) in both fist-line and second-line settings. These treatments rarely yield complete responses and are not curative [77].
The European Association of urology Guideline Panel assert that while talking about mRCC, surgery is curative only if all the tumor burden can be removed. Retrospective data suggest that this goal is achievable in patients with single- or oligometastatic disease that is amenable to surgery. Cytoriductive nephrectomy (CN) is recommended in mRCC patients with good PS, large primary tumors, and low metastatic volumen. Chemotherapy is not effective for clear cell mRCC. Recent advances in molecular biology have led to the development of several novel agents for treating mRCC. As consequence, monotherapy with IFN-alpha or high-dose bolus interleukin (IL)-2 should no longer be routinely recommended as first line therapy in mRCC [78].

Prognosis

A study of 101 patients that underwent resection of metastasis (35 patients for 2 times and 6 patients for 3 times). Median survival after the initial metastasectomy was 28 months. Initial tumor stage, grade or size were not related to metastasis location or survival. Patients with solitary metastases did not show longer survival after the first metastasectomy compared to no solitary lesions. Disease free survival was found in 14 and 7%, with follow-ups of at least 45 and 60 months, respectively. The longest survival was found after surgery for pulmonary lesions [79]. Nonetheless, H. Itoh et al., stated that if there are multiple distant metastases, the prognosis is worse than in a case with a solitary metastasis. Resection of a solitary metastasis was associated with a 5-year survival rate of 34% in 59 cases, which is exactly the same rate as following nephrectomy in the absence of apparent metastases [28]. When metastases are synchronous, the odds of survival worsen, and most patients die within 1 year [31]. Won JY et al., in their case series of metastatic disease to the gallbladder, found that the only factor associated with prolonged survival was a R0 resection and presentation with acute cholecystitis was associated with poor survival [38]. The five-year survival and median disease-free time are twice as long after metastasectomy (88% and 44 months respectively) [49].

Long-term survival data for gallbladder metastases are not available as there are so few cases reported but a large study from the Memorial Sloan-Kettering Center on survival after metastasectomy for all renal cell carcinoma metastases, found that patients who had a curative resection of metastases had a five-year survival rate of 44%. According to them, favorable features for survival were a disease free interval greater than 12 months versus 12 months or less (55% vs 9% e-year overall survival [OS] rate, p<0.0001), solitary versus multiple sites of metastases (54%-% vs 29% 5-year OS rate, p<0.001) and age younger than 60 years (49% vs 35% 5-year OS rate, p<0.05) [53].

How to behave before a gallbladder intraluminal neoplasm

Gallbladder polyps are relatively common and found in up to 5% of the adult population. Most polyps are benign in the form of cholesterol polyps or adenomas, but, a small percentage are malignant [53].

The size of the polypoid lesion, with a diameter of 10 mm as the cutoff point, has been proposed as a criterion for differential diagnosis between benign and malignant polyp lesions of the gallbladder. The prevalence of malignancy varies between 37-88% in polyps that exceed 10 mm. Patients with asymptomatic intraluminal neoplasm less than 5mm in diameter should be followed sonographically at intervals of 3-6 months to establish growth rates. Regarding surgery, patients with symptomatic polypoid lesions to the gallbladder should undergo surgery regardless of the size of polypoid lesion.

Terzi et al., proposed 3 risk factors that increase the probability that a polyp may be malignant: (1) age >60 years, (2) size of polyp (>10mm), and, (3) coexistence of gallstones.

They suggest surgery in the presence of one of the risk factors [28,80]. Some surgeons advise the use of laparoscopic cholecystectomy for elective cholecystectomy. However, open cholecystectomy is recommended for polyps larger than 18mm in size because of the risk of invasion of surrounding structures by malignancy [81].

A Cohrane Review stated that the management of gallbladder polyp is still controversial. Cholecystectomy for polyps larger than 10 mm has been recommended because of the association between polyps larger than 10 mm and gallbladder cancer. Cholecystectomy is often recommended for patients with biliary type pain and polyps smaller than 10 mm. There has been no randomized clinical trial comparing cholecystectomy with observation for gallbladder polyps [82].

Conflicting interests

The authors have declared that no conflict of interests exist.

Acknowledgements

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Abbreviations

RCC: renal cell carcinoma; ccRCC: clear cell renal cell carcinoma; mRCC: metastatic renal cell carcinoma; US:
ultrasound; CT: computed tomography; MRI, magnetic resonance imaging; CEUS: contrast enhanced ultrasound; PET: positron emission tomography; OS: overall survival; GB: gallbladder; CRN: cytoreductive nephrectomy.

Author contributions

C.R.C. conceived the idea of the review, analyzed the literature and contributed to the lay out of the paper. Read and approved the final manuscript. Z.M. analyzed the literature, contributed with the data analysis, and the lay out of the paper. Read and approved the final manuscript. U.L. analyzed the literature, contributed with the data analysis, analyzed the result and gave a final input to the work. Read and approved the final manuscript. A.G. analyzed the results and gave his final input to the work. Read and approved the final manuscript. P.C. analyzed the results and gave his final input to the work. Read and approved the final manuscript.

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