REVIEW ARTICLE

Surgical Resection of Urological Tumor Metastases Following Medical Treatment

Axel Heidenreich, Stefan Wilop, Michael Pinkawa, Daniel Porres, David Pfister

SUMMARY

Background: The rate of systemic metastases is about 20% in testicular germ cell tumors, 25% to 30% in prostate cancer, 30% in urothelial carcinoma with muscle invasion, and 50% in renal-cell carcinoma. This article is a critical review of current data on the resection of metastases of urological tumors after systemic drug treatment.

Methods: Review of pertinent publications retrieved by a selective literature search.

Results: No pertinent prospective, randomized trials, meta-analyses, or Cochrane reviews have been published. The publications available for review include guidelines and retrospective studies with evidence levels ranging from IIB to III. For non-seminomatous germ cell tumors with tumor markers that are negative or have reached a plateau after chemotherapy, resection of retroperitoneal, intra-abdominal, and intrathoracic metastases with curative intent is now the treatment of choice at clinical reference centers. For urothelial carcinoma that has gone into partial remission after systemic chemotherapy, with full resectability, the resection of metastases prolongs survival from about 13 months to 31–41 months. For prostatic carcinoma with solitary, intrapelvic lymph-node metastases and PSA less than 4 ng/mL, the resection of metastases prolongs 5-year progression-free survival in 40% to 50% of cases. There is, however, no indication for the resection of retro-peritoneal, visceral, or bony metastases. In renal-cell carcinoma, the resection of pulmonary or hepatic metastases is associated with a 5-year survival rate of 40% to 50% or 62%, respectively, and should thus be made a component of the treatment plan for this disease. The indication for resecting metastases of urological cancers should always be established by an interdisciplinary tumor board in the light of the existing scientific evidence.

Conclusion: The resection of metastases of some types of urological cancer after chemotherapy can prolong progression-free and overall survival. This form of treatment deserves consideration as a component of individual care and of the interdisciplinary treatment plan for urological cancers.

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Except in the case of testicular germ cell tumors, with urogenital neoplasms there is uncertainty as to when and how extensively to resect metastases after systemic medical therapy, and what prognostic benefit may be gained from it. In the European evidence-based guidelines this surgical procedure is referred to as a therapeutic option on an individual basis, if it is supported by biopsy and the metastases are not curable by other, nonsurgical means such as consolidated radiotherapy (1–5). This review article presents a critical evaluation of the current data with the aim of developing a treatment algorithm for urological tumor entities.

The main procedures used for metastatic renal cell carcinoma and for germ cell tumors are, respectively, cytoreductive radical nephrectomy and inguinal orchiectomy, while for prostate carcinoma and muscle-invasive urothelial carcinoma, radical prostatectomy and radical cystectomy are respectively the first-line treatments if imaging shows absence of metastases.

Patients and methods

A selective literature search was carried out in the Medline, Embase, and Web of Science databases to identify original articles, reviews, and editorials on the topic “surgical resection of metastases of neoplasia of the urogenital tract.” All articles published between 1990 and 2012 in peer-reviewed journals were considered.

In the literature search, the parameters renal cell carcinoma, urothelial carcinoma, urinary bladder carcinoma, prostate carcinoma, and testicular germ cell cancer were linked with the variables metastasis, lung metastases, liver metastases, lymph node metastases, pancreatic metastases, and bone metastases, and the search terms metastasectomy, metastasis surgery, and lymphadenectomy. All the search terms are contained in the database of Medical Subject Headings (MeSH). The current European and national guidelines were also included for consideration. The assessment of evidence levels and recommendation grades of the works cited followed the Oxford classification (6, 7).

Testicular germ cell tumors

Surgical resection of retroperitoneal, intra-abdominal, or intrathoracic metastases after systemic chemotherapy is performed with curative intent as a basic component of the interdisciplinary, multimodal treatment of advanced nonseminomatous germ cell tumors

Department of Urology, University Hospital Aachen:
Prof. Dr. med. Heidenreich, Dr. med. Porres, Dr. med. Pfister

Department of Hematology and Oncology, University Hospital Aachen: Dr. med. Wilop

Department of Diagnostic and Interventional Radiology, University Hospital Aachen:
PD Dr. med. Pinkawa

All departments collaborate in the Euregional Comprehensive Cancer Care Center Aachen (ECCA).

TABLE 1

Adjunctive surgical procedures in a consecutive cohort of 158 patients after post-chemotherapy retroperitoneal lymphadenectomy (e7)

Procedure	n (%)
Inferior vena cava resection	4 (2.5)
Inferior vena cava prosthesis	3 (1.9)
Inferior vena cava thrombectomy	2 (1.3)
Resection and replacement of aorta	2 (1.3)
Nephrectomy	6 (3.8)
Resection and reconstruction of ureter	4 (2.5)
Bowel resection	6 (3.8)
Liver metastasectomy	8 (5.0)
Resection of retrocrural lymph nodes	8 (5.0)
Total	43 (27.2)

(NSGCTs) (1, e2). Residual tumors in advanced seminoma are treated with surgery, radiotherapy, or cytotoxic agents only if F18-FDG-positron emission tomography (FDG-PET/CT) suggests the presence of active foci in the residual tumors or they have been confirmed by biopsy ([1, 8], evidence level [EL] IIA).

Nonseminomatous germ cell residual tumors that are larger than 1 cm and whose morphology can be visualized on CT are in all cases surgically resected with the aim of achieving complete resection, irrespective of their location or size ([1, 9], EL IIA). Histological analysis of large residual tumors shows an active carcinoma in about 15% to 20% of cases and a mature teratoma in 30% to 40%. Residual tumor resection (RTR) is a surgically complex operation that in up to 25% of cases requires the resection of adjacent organs and vascular structures (*Table 1, Figure 1a–c*) (e3, e4). Complication rates and recurrence and survival rates depend on the experience of the surgeon (10, 11).

Locoregional retroperitoneal recurrences after RTR as associated with a survival rate that is reduced by about 30%, from 84% to 55%, compared with a recurrence-free course ([e5–8], EL IIB). In accordance with the current guidelines, therefore, RTR requires precision in the preoperative planning, if necessary with interdisciplinary collaboration, and should only be carried out at experienced centers ([10, 11], EL IIA). In a retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database, Capitanio et al. (10) showed a significantly increased 90-day postoperative mortality of 6% in less experienced centers compared to 0.8% in reference centers. In an evaluation of 151 patients undergoing RTR, Fléchon et al. (11) documented significantly higher compliance with guidelines among experienced than among less experienced surgeons in terms of their selection of patients for RTR

and performance of the operation, leading to a higher rate of complete resection and a lower recurrence rate.

Concomitant pulmonary residual tumors should, depending on their number and size, be resected, because in up to 35% of cases their pathohistology is shown to be discordant with the retroperitoneal finding ([1, e9], EL III). Because the histological discordance between the two lungs is only 5%, the decision for or against surgical resection of contralateral metastases may be made dependent on the histology of the first procedure (e9).

The decision whether to resect synchronous liver metastases depends on the histology of the retroperitoneal metastases. In current series there is a 94% concordance between the histological findings when the retroperitoneal residual tumors show a scar or necrosis, so in this situation aftercare is given. In all other patients, complete resection is the goal ([1, e10], EL III).

How to manage residual tumors that are smaller than 1 cm is the subject of much debate because of their low recurrence rate when the patient is kept under active surveillance ([e11–e14], EL IIB). In retrospective studies, recurrence rates of 6% to 9% were shown at the end of a post-observation time of 42 months and a tumor-related mortality of 3% at 15.5 years (18, 19). Significant differences in progression-free survival are shown between patients with a favorable (95%) and those with an intermediate or unfavorable prognosis (73%) according to the International Germ Cell Cancer Collaboration Group (IGCCCG) classification.

In contrast to these are retrospective surgical studies that have shown a mature teratoma or active carcinoma in up to 50% of patients even with small residual tumors (e13, e14). In the current guidelines there is a consensus to the effect that patients with small residual tumors, normalized tumor marker concentrations, no evidence of a mature teratoma in the primary tumor, and a favorable prognosis in the IGCCCG classification should be actively observed, whereas all other patients—including those who have had high-dose chemotherapy with stem cell transplantation—should undergo resection. 18F-FDG-PET is not indicated for nonseminomas, since scar/necrosis and a mature teratoma show the same low metabolic index and cannot be distinguished in the differential diagnosis.

Urothelial carcinoma of kidney, ureter, and urinary bladder

Between 5% and 35% of patients with muscle-invasive urothelial carcinoma of the urinary bladder develop locoregional or systemic recurrence after radical cystectomy ([12, 13], EL IIB). The standard treatment consists of systemic chemotherapy with gemcitabine and cisplatin, which leads to partial or complete remission in 70% of patients ([14], EL I). The mean progression-free interval is 7 months, and mean survival time is just under 14 months. Recurrences occur mainly at the site of the primary metastasis, indicating persistence of active cancerous cells, so there is a rationale for metastasectomy to improve the prognosis ([15–21], EL III).

Recent results are available for retrospective analyses of 274 patients that document an improvement in mean survival to 31 to 41 months (Table 2). The Urological Oncology Working Group (*Arbeitsgemeinschaft Urologische Onkologie*, AUO) analyzed the oncological and surgical results of residual tumor resection in 41 patients with metastatic unifocal or multifocal urothelial carcinoma who had responded at least partially to MVAC (methotrexate–vinblastine–doxorubicin–cisplatin) or gemcitabine–cisplatin chemotherapy (21). Mean overall survival from first diagnosis of the metastatic urothelial carcinoma and from metastasectomy was 38 months and 34 months respectively, with 5-year survival rates of 28% and 29% respectively. Mean tumor-specific survival was 46 months and 41 months respectively, while recurrence-free survival was 20 and 19 months respectively.

The comparable mean survival time after the therapeutic alternative of salvage chemotherapy is 7 to 10 months ([22], EL IIA). Metastasectomy for advanced urothelial carcinoma is currently to be regarded as a therapeutic option on a case-by-case basis; it should be used only in the setting of a multimodal treatment plan and is in competition, especially in multimorbid patients, with high-conformity radiotherapeutic methods such as stereotactic radiotherapy. An essential prerequisite for long-term control after metastasectomy is significant response to the primary systemic chemotherapy and complete resectability of all metastases (EL III).

Prostate carcinoma

Urologists and oncologists are increasingly being faced with the request for salvage metastasectomy, now that modern diagnostic imaging methods such as choline PET/CT in patients with low-PSA (prostate-specific antigen) recurrence are often enabling early diagnosis of “isolated” metastases (23). The possibility of resecting presumed “isolated” metastases raises patients’ hopes of cure, so the decision for surgery requires a very critical frame of mind.

Salvage metastasectomy is the term used to describe surgical treatment of locoregional or solitary systemic metastases, confirmed by imaging, after local primary therapy or systemic androgen deprivation. In prostate cancer, the aim of salvage metastasectomy is not primarily to prolong life, but to gain time before having to initiate systemic androgen deprivation, which is associated with marked side effects and the therapeutic effects of which are time-limited.

Because of the associated limited life expectancy, visceral and bone metastases should be surgically resected or, alternatively, treated by radiotherapy only if the patient has symptoms that cannot be controlled by conservative management or if function is threatened.

If lymph node metastasis is demonstrated after primary local therapy, a surgical procedure to aid differential diagnosis may be considered if the lymph node involvement is minimal and PSA doubling time is slow ([24], EL IIB). Rigatti et al. (24) showed in a group of

Figure 1: Surgical site in a patient undergoing post-chemotherapy retroperitoneal lymphadenectomy (RPLA)

- a) Retroperitoneal residual tumor with cystic and solid components indicating a mature teratoma; a long segment of the abdominal aorta has been surrounded
- b) Preparation of the renal hilum and infrahilar aorta
- c) Site after complete tumorectomy and placement of aortic prosthesis

TABLE 2

Results of metastasectomy in urothelial carcinoma of the upper and lower urinary tract

Reference	n	Site of metastases	Progression-free survival	Mean survival	5-Year survival rate
Cowles et al. (15)	6	Lung	58 months	5 years	–
Dodd et al. (16)	50	Lymph nodes	n.d.	46 (32–79) months	33%* ¹
Miller et al. (17)	55	Lymph nodes, lung, liver	15 months	17 months	33% (2 years)
Herr et al. (18)	80	Lung, lymph nodes	–	9 months to 5 years	58% pCR* ¹ 41% cCR* ¹
Sweeney et al. (19)	11	Lymph nodes	7 months	14 months	36% (4 years)* ¹
Siefker-Radtke et al. (20)	31	Lung, lymph nodes, brain	7 months	31 months	33%
Lehmann (21)	41	Lymph nodes, lung, other	19 months	41 months	29%

Prognostic factors: *¹ long-term therapeutic benefit only in patients who responded significantly to chemotherapy; pCR, pathological complete remission; cCR, clinical complete remission; n.d. no data

72 patients that those with a PSA value below 4 ng/mL, and lymph node involvement that was predominantly intrapelvic and did not involve the retroperitoneal lymph nodes, just under 50% of patients remained recurrence-free after 5 years and benefited from this kind of surgery. In all other situations, the progression-free interval is very short and the therapeutic value doubtful.

In all, four other working groups have reported on the oncological results of pelvic and retroperitoneal salvage lymphadenectomy, with similar oncological findings ([e14–e18], EL III). The mean progression-free interval was 2 years; no conclusions can be drawn about overall survival. A PSA value above 4 ng/mL, rapid PSA doubling time, and a large number of suspect lymph nodes on imaging are associated with rapid post-operative progression and represent a relative contra-indication to surgery ([24, e14–e17], EL III).

Renal cell carcinoma

About 20% of patients show locoregional or systemic metastases at the time of diagnosis (25). After radical nephrectomy, up to 30% develop metastases in the postoperative period (3). With metastatic renal cell carcinoma, treatment with bevacizumab, multi-targeted tyrosine kinase inhibitors, or mTOR inhibitors is the therapy of choice; after sequential treatment this leads to a mean survival of 34 months (3). At the time of metastasization, 55% of patients show metastases in more than two organ systems; 30% and 15% of patients respectively show metastases in two organ systems or one organ system (3, 25, 26). Lung and lymph node metastases are the most frequent (62% to 77% and 34% to 58% of cases respectively), while the skeletal system and liver are involved in 18% to 30% of cases (3, 26).

Despite the advances in molecularly targeted medical therapy, curative long-term remission of metastatic lesions is not achieved, and for this reason the international guidelines recommend radical tumor nephrectomy with metastasectomy when

- 1) metastatic findings have remained stable for at least 3 months after systemic therapy,
- 2) the metastases at all locations can be completely resected, and
- 3) any possible complications of surgery stand in reasonable relation to the potential benefit for the patient ([3, 27, 28], EL IIB–III).

Lung metastases make up around 60% to 70% of all metastases of renal cell cancer and represent an indication for surgical resection because of the improvement this brings in tumor-specific survival (3, 25). In the past 15 years, various working groups have shown that complete resection of all existing lung metastases leads to a 5-year survival rate of 40% to 50% and a mean survival between 35 and 55 months, with low surgical mortality and morbidity rates (0% to 2% and 1.5% to 10% respectively) (Table 3) ([29–32, e19–e22], EL IIB).

The following risk factors are associated with a favorable oncological result and favor metastasectomy:

- interval of ≥ 2 years between radical nephrectomy and demonstration of lung metastases
- complete resection
- ≤ 6 metastases
- diameter of metastases < 4 cm, and
- no evidence of mediastinal lymph node metastases ([31, 32], EL IIB).

Alternatively, if metastasization is oligotopic (1 to 4 sites), stereotactic imaging-guided hypofractionated radiotherapy or radiosurgery may be given. The question of whether adjuvant systemic therapy is needed is currently being investigated in the prospective randomized SMAT study.

Liver metastases are reported in up to 40% of patients with metastatic multilocular renal cell carcinoma; in around 5% the liver is the only organ affected by metastases (3, 25). Liver metastasectomy is a safe, effective treatment with the possibility of long-term survival, or in some cases even cure. In current series, low postoperative mortality and complication rates

TABLE 3

Treatment-related complications after metastasectomy in various sites (Clavien classification)

Procedure	Clavien grades I–III	Clavien grade IV	Clavien grade V
RTR*	Retrograde or anejaculation in 10% to 15%	Vascular complications 3% to 5% Obstructive ileus 2% to 2.5% Chylous ascites 1% Ureteral lesion 1% to 1.5%	0.5%*
Liver metastasectomy	15% to 20%	Total: 10% to 32% Pulmonary embolism Intra-abdominal bleeding Intra-abdominal abscess Biliary fistula Cardiovascular complications	3% to 5%
Pancreatic metastasectomy	Superficial wound infection 5% to 15% Pneumonia 3% to 6%	Postoperative infection 5% to 10% Pancreatic fistulas 5% to 9% Sepsis 2% to 3%	3% to 5%
Pulmonary metastasectomy	3% to 5%	<1%	0%
Lymphadenectomy	15% to 20%	Total: 5% Intra-abdominal bleeding Chylous ascites Obstructive ileus	0%

RTR, post-chemotherapy residual tumor resection in testicular cancer; * in experienced centers

between 16% and 20% are reported ([33, e23–e25], EL III). Solitary, metachronous liver metastases, a metastasis diameter below 5 cm, a progression-free interval of more than 2 years from nephrectomy to evidence of liver metastases, and a good general condition of the patient (Eastern Cooperative Oncology Group [ECOG] 0–1) are favorable prognostic factors. Mean survival is reported as 50 to 155 months, compared to 17 to 31 months in the presence of unfavorable prognostic factors.

In the largest series published to date, Stähler and colleagues ([33], EL IIB) presented the therapeutic effect of liver metastasectomy compared to a matched control group of patients treated with systemic therapy alone. While the mean survival and 5-year survival rate in the surgical group were 142 months and 62% respectively, the medical group showed a mean survival of only 27 months and a 5-year survival rate of 29%. Alternatively, in patients with oligotopic symptomatic metastases, radiotherapy or radiofrequency ablation may be used.

Pancreatic metastases of renal cell carcinoma (RCC) are rare and are associated with synchronous extrapancreatic metastases in 22% of cases and metachronous extrapancreatic metastases in 58% of cases (3, 25).

A recent review article compared treatment results in 321 patients given surgery and 73 patients treated medically ([34], EL IIB). Metastasectomy was associated with a low complication rate and an operative mortality rate of 2.8%. Overall survival at 2 and 5 years after resection was 76% and 57% respectively, which was significantly better than in the nonsurgical group (41% and 14% respectively). Unfavorable prognostic factors for long-term therapeutic success were an interval of 2 years or less from radical nephrectomy to

evidence of metastasization, synchronous extrapancreatic metastases, and the presence of symptomatic pancreatic metastases, so where any of these are present, metastasectomy is not indicated (34, e26).

Cerebral metastases occur in 4% to 17% of patients (3, 25). Renal cell carcinoma is the third most frequent origin of brain metastases, after bronchial and breast carcinoma. Available therapeutic options are:

- neurosurgical metastasectomy
- whole-brain irradiation
- stereotactic radiosurgery, and
- a combination of the above ([35–37], EL IIB–III).

These options improve quality of life and life expectancy compared to supportive/palliative treatment alone. Which treatment to choose depends on individual patient-related factors such as tumor size and location, number of metastases, and the patient's general condition. In every case, intensive interdisciplinary discussion is essential for appropriate treatment planning.

Whole-brain irradiation is associated with prolongation of life by an average of 3 to 6 months, and is used with palliative intent in patients with multilobar brain metastases (35, 36).

Neurosurgical resection is indicated for solitary, easily accessible, necrotic metastases of low radiosensitivity. The disadvantage is the intracranial recurrence rate, which can be up to 50%, so in many cases resection is combined with whole-brain irradiation.

Stereotactic radiosurgery is performed in patients with oligotopic (≤ 4) solid brain metastases up to 3 cm in diameter, which are treated with high single doses of ≥ 20 Gy, usually without impairing the patient's quality of life (35–37).

Mean survival in patients with isolated brain metastases without associated extracranial metastases is reported at around 15 months, compared to only 5 months when associated metastases are present (35, 36). Other risk factors associated with a favorable outcome are the patient's general condition and the interval from nephrectomy to demonstration of metastases.

Conflict of interest statement

Dr. Pfister has received lecture fees and is a member of the Advisory Board of Astellas IPSEN and Sanofi Aventis.

Prof. Heidenreich has received lecture fees and is a member of the Advisory Board of AMGEN, Astellas, Bayer AG, GlaxoSmithKline, IPSEN, Janssen-Cilag, Pfizer, Sanofi Aventis, and Takeda.

Dr. Pinkawa, Dr. Porres and Dr. Wilop declare that no conflict of interest exists.

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KEY MESSAGES

- 30% to 50% of metastatic nonseminomatous germ cell tumors show residual metastases after chemotherapy. Post-chemotherapy resection of retroperitoneal, intra-abdominal, and intrathoracic residual tumors larger than 1 cm in patients with negative tumor markers or a tumor marker plateau, performed in experienced reference centers, is the therapy of choice with curative intention (evidence level IIA).
- Around 30% of bladder carcinomas develop systemic metastases after radical cystectomy. Metastasectomy after systemic chemotherapy in patients with urothelial carcinoma, if partial remission is achieved and all residual tumors can be completely resected, leads to an improvement in overall survival to 31 to 41 months (evidence level III). Metastasectomy is performed with curative intent in well-chosen patients.
- Around 30% of prostate carcinomas develop metastases after local primary therapy. Metastasectomy in prostate carcinoma, if the metastases are solitary, intrapelvic lymph node metastases and the patient's PSA value is below 4 ng/mL, lengthens the progression-free interval (evidence level III). Metastasectomy is performed as a palliative procedure to avoid systemic androgen deprivation. There is no evidence to support the resection of metastases in other organs.
- Around 20% and 30% of renal cell carcinomas show metastases at the time of diagnosis or develop metastases after radical nephrectomy. In renal cell carcinoma, metastasectomy may be performed with curative intent; compared with systemic therapy alone, it is associated with a survival advantage in patients with lung and liver metastases and leads to 5-year-survival rates of 40% to 50% and 62% respectively (evidence level IIB).
- For correct selection of patients with any of the tumor entities discussed above to undergo metastasectomy, an interdisciplinary tumor board discussion is essential.

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Corresponding author

Prof. Dr. med. Axel Heidenreich
Universitätsklinikum der RWTH Aachen
Pauwelsstr. 30, 52074 Aachen, Germany
aheidenreich@ukaachen.de

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