REVIEW

OPEN

Role of surgical consolidation in metastatic urothelial carcinoma

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Purpose of review
Since the development of systemic combination chemotherapy, postchemotherapy extirpation has been performed in selected patients mainly with locally advanced and/or initially unresectable bladder cancer, and, in very selected patients, surgical consolidation for visceral metastases has also been performed. The purpose of this article was to review and summarize the current evidence for the role of surgical consolidation in metastatic urothelial carcinoma.

Recent findings
The role of metastasectomy has not yet been examined in a randomized setting. In terms of locally advanced and/or node-positive bladder cancer, studies further support the benefit of surgical consolidation, especially after a favorable response to systemic chemotherapy. Regarding metastasectomy for visceral metastasis, recent evidence suggested that lung metastases (ideally small solitary lesions) are a good indication.

Summary
Patients with a good response to chemotherapy, limited nodal/pulmonary disease, and a favorable performance status are good candidates for surgical consolidation. Careful patient selection is mandatory.

Keywords
metastasectomy, metastatic urothelial carcinoma, surgical consolidation, systemic chemotherapy

INTRODUCTION

Systemic chemotherapy continues to be the mainstay in the treatment of advanced metastatic urothelial carcinoma, and, based on a randomized trial demonstrating similar survival but a favorable toxicity profile compared with the methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) regimen, the combination of gemcitabine and cisplatin has now become a standard first-line chemotherapy [1]. Although initial response rates to modern cisplatin-based combination regimens have been reported to be around 50–70%, the effects are usually transient, and most patients with a favorable response will eventually develop disease progression. So far, although second-line chemotherapy regimens have been studied, such as taxane-based systemic chemotherapy [2–5], and, in Europe, vinflunine is allowed to be used for platinum-resistant metastatic urothelial carcinoma [6,7], the salvage strategy has yet to be fully established.

In terms of an aggressive surgical approach, the combination of systemic chemotherapy and surgical extirpation has been performed in selected patients mainly with locally advanced and/or initially unresectable bladder cancer, and the outcomes have been reported [8–16]. Regarding metastasectomy to visceral organs in metastatic urothelial carcinoma patients, Cowles *et al.* [17] firstly reported surgical outcomes in patients with lung metastasis of urothelial carcinoma. They observed a median of 5-year survival in six patients after the removal of a solitary lung metastasis without systemic chemotherapy. Since then, surgical consolidation for visceral metastases has also been performed in selected patients, and its beneficial role was anecdotally reported [18–28]. In the present study, we reviewed the current evidence in terms of an aggressive surgical approach to advanced urothelial carcinoma, and

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KEY POINTS

- The role of metastasectomy has not yet been examined in a randomized setting.
- Each study group has offered surgical consolidation to metastatic urothelial carcinoma patients according to their own guidelines, and there are many things in common, such as a good response to systemic chemotherapy, limited disease, the feasibility of resection, and a favorable performance status. Careful patient selection is mandatory.
- Regarding metastasectomy for visceral metastasis, recent evidence suggested that lung metastases (ideally a small solitary lesion) would be a good indication.

summarized the present recommendations regarding decision-making.

INDICATION OF METASTASECTOMY FOR METASTATIC UROTHELIAL CARCINOMA

At present, there are no strict criteria regarding the indications of surgical consolidation for metastatic urothelial carcinoma, and the role of metastasectomy has not yet been examined in a randomized setting. Although each study group considered surgical consolidation based on their own guidelines, they have many things in common. In the M.D. Anderson Cancer Center group, they consider metastasectomy when the patients demonstrate a good response to systemic chemotherapy, have metastasis at the initial or a single site, have a disease which is considered resectable with a negative surgical margin, and show a stable disease without rapid progression [18]. In a German multi-institutional study, Lehmann *et al.* [19] stated that surgical consolidation remains investigational and should be offered when the disease is limited and shows a favorable response to systemic chemotherapy, and surgical consolidation of all detectable disease seems feasible. Our group also performed surgical consolidation in extremely selected patients, and reported the outcomes [20,21]. Figure 1 shows actual computed tomography (CT) images in the patients undergoing surgical consolidation. We usually considered surgical consolidation in the situation whereby the disease was restricted to a single organ, the number was ideally one, and the patient had a good performance status and showed a good response to systemic chemotherapy [20]. Herr [29] also listed pivotal points regarding patient selection in his editorial comment on the study by Lehmann *et al.* as follows:

(1) Systemic chemotherapy first, because it works for patient selection, and the extent of surgery.
(2) Consider surgical consolidation in patients with a good response (complete or partial) to systemic chemotherapy. Regarding postchemotherapy radiological images, it is difficult to distinguish patients from those without remaining viable cancer. Although PET is promising in the postchemotherapy treatment decision regarding testicular seminoma [30–33], its role in urothelial carcinoma is investigational at present [34,35].
(3) Surgical salvage without systemic chemotherapy is extremely rare.
(4) Limited nodal or a single pulmonary or single visceral lesion would be a good indication. In contrast, for example, multiple liver metastases or metastases involving two or more site organs or bone metastases are not favorable.
(5) Surgery must be technically feasible.
(6) A potential patient needs a strong motivation for aggressive treatment, and a good health status.

Regarding the salvage outcomes in patients who failed to respond to first-line chemotherapy, Otto *et al* [36]. reported an unfavorable prognosis in a study of 70 patients refractory to the MVAC regimen. Most patients had multiple metastases (76%, 53/70) involving multiple organs (41%, 29/70), the median survival time was 7 months, and the 1 and 2-year survival rates were 30.7 and 19.3%. In 83% of the symptomatic patients (42/51), surgery improved their performance status, whereas asymptomatic patients complained of a reduced quality of life after surgery. A perioperative mortality rate of 4% (3/70) was also observed. On the basis of these observations, they concluded that metastasectomy for disease refractory to systemic chemotherapy had an impact on the quality of life of symptomatic patients only, and offered no survival advantage.

Taken together with these opinions, surgical consolidation should be currently considered in patients with a good response to systemic chemotherapy, stable disease after chemotherapy, oligometastasis ideally limited to a single site, a good health status, and a strong motivation for aggressive treatment. In the following paragraphs, we reviewed the specific treatment outcomes according to metastatic sites.

POSTCHEMOTHERAPY SURGERY IN PATIENTS WITH INITIALLY UNRESECTABLE OR NODE-POSITIVE BLADDER CANCER

A rationale of postchemotherapy surgery is the high likelihood of relapse at the initial disease sites.

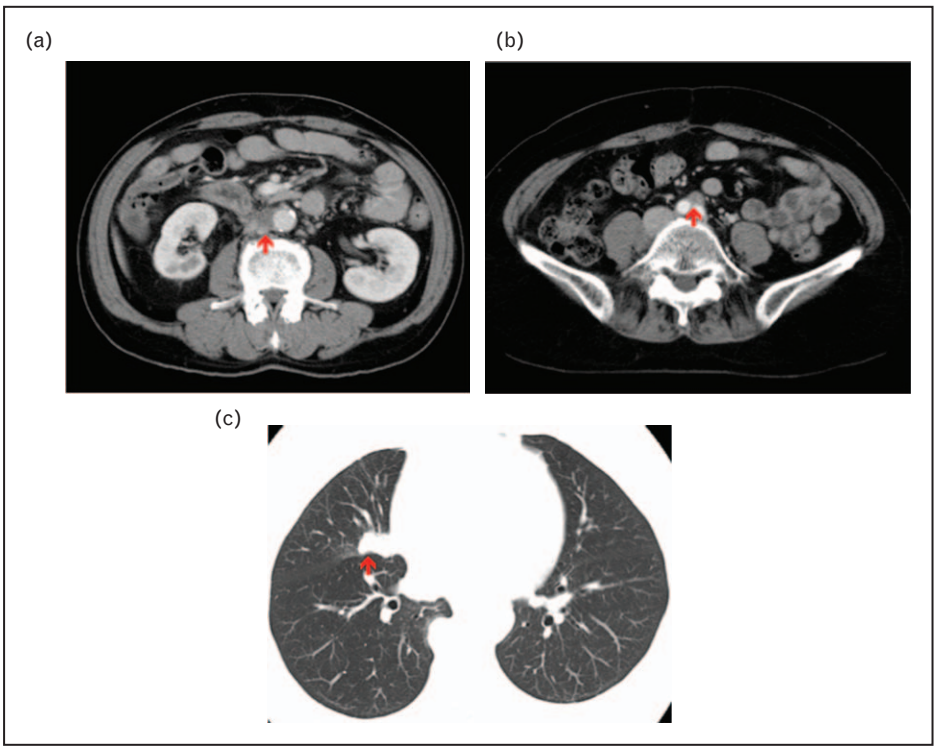

FIGURE 1. (a) A 61-year-old male with right renal pelvic carcinoma. He initially presented with massive retroperitoneal lymph node and lung metastases. After seven courses of first-line chemotherapy, the lung metastases disappeared, lymph node metastases reduced (arrow), and retroperitoneal lymph node dissection in conjunction with right nephroureterectomy was performed. The pathology revealed viable cancer. He developed lymph node recurrence 1 month after metastasectomy, and died 12 months after metastasectomy. (b) A 55-year-old female patient with right ureteral carcinoma. She initially presented with massive retroperitoneal lymph node metastasis. At the time of her first surgery (nephroureterectomy) after three courses of first-line chemotherapy, retroperitoneal lymph node dissection was aborted because it was considered unresectable. After second-line chemotherapy (paclitaxel-based regimen), lymph node metastases reduced (arrow), and surgical consolidation was achieved. The pathology revealed necrotic cells. She developed bone metastasis 16 months after metastasectomy, and died 31 months after metastasectomy. (c) A 63-year-old woman. She developed solitary lung metastasis (arrow) 2 years after left nephroureterectomy. Right lobectomy was initially performed, and, after pathological confirmation of metastatic urothelial carcinoma, two courses of gemcitabine and cisplatin combination regimen were administered. She remains disease-free 38 months after metastasectomy.

Dimopoulos *et al.* [37] previously reported the relapse pattern and its outcome in the analysis of 58 patients who developed relapse after a complete response (CR) or partial response (PR) induced by cisplatin-based systemic chemotherapy. The median interval from the maximum effect of chemotherapy to disease relapse was about 9 months (range 3–53), and, of the patients who initially presented with locoregional disease ($n = 42$), 74% (31/42) showed recurrence with the same pattern without distant disease. On the basis of these observations, they speculated on the possible role of local therapy (surgical consolidation or radiotherapy) after a maximum response to systemic chemotherapy.

So far, several retrospective studies have shown improved outcomes in patients with initially unresectable or regional node-positive bladder cancer following postchemotherapy surgery. Table 1 summarizes the outcomes of metastasectomy for locally advanced and/or nodal disease. Donat *et al.* [8] reported that, in 41 patients with locally advanced bladder cancer initially treated by MVAC chemotherapy, postchemotherapy surgery was completed in 24 patients. On pathological examination, no viable cell remained in 33% (8/24) of patients. Regarding the survival outcomes, of the 14 patients with clinical CR, eight underwent subsequent cystectomy, five refused surgery, one had unresectable tumor at surgery, and 50% (7/14) survived. On the contrary, of the 27 nonresponders, 16 underwent cystectomy, 11 did not due to unresectable tumor, and 7% (2/27) survived. In addition, of the five patients with clinical CR who refused postchemotherapy surgery, only one patient survived. Their observations indicated that surgical consolidation

Table 1. Treatment outcomes of metastasectomy for locally advanced and/or nodal disease

Study (year)	No. of patients	Resected sites	Chemotherapy responses	Pathology	Outcome	Reference
Donat *et al.* (1996)	41[a]	Initially unresectable primary tumor: $n=23$, lymph nodes or abdominal/pelvic mass: $n=18$	CR (34%, 14/41), IR (66%, 27/41)	pT0pN0 33% (8/24)	Median OS 20 months from the start of chemotherapy	[8]
Herr *et al.* (2001)	80	Initially unresectable primary tumor: $n=32$, extensive regional pelvic nodal metastasis: $n=31$, distant retroperitoneal metastasis: $n=17$	CR (30%, 24/80), PR (55%, 44/80), NC (15%, 12/80)	pT0pN0 30% (24/80)	Of the 24 patients who achieved pathological CR, 58% (14/24) survived. Of the 49 patients who achieved surgical CR, 41% (20/49) survived.	[9]
Meijer *et al.* (2013)	125	Locally advanced and/or lymph node-positive bladder cancer	Actual number of patients regarding chemotherapy responses was not described.	Complete pathological response was observed in 26.3% of patients.	5-year OS 54% for pathological CR and 33% for pathological PR patients from the start of chemotherapy	[10]
Sweeney *et al.* (2003)	11	Retroperitoneal lymph nodes: $n=11$	CR (64%, 7/11), PR (36%, 4/11),	Nine patients (82%, 9/11) had residual disease in the retroperitoneal nodal fields.	4-year DSS 36% from metastasectomy	[11]
Kim *et al.* (2004)	3	Retroperitoneal lymph nodes: $n=3$	PR (100%, 3/3)	pN0 33% (1/3)	3-year DSS 33% from metastasectomy	[12]
De Vries *et al.* (2008)	14	Supraregional lymph nodes: $n=14$	CR (36%, 5/14), PR (64%, 9/14),	pT0pN0 29% (4/14)	5-year DSS 24% from metastasectomy	[13]
Childs *et al.* (2010)	4	Retroperitoneal lymph nodes: $n=4$	CR (50%, 2/4), SD (50%, 2/4),	Two patients (50%, 2/4) had residual disease in the surgical specimens.	5-year DSS 50% from metastasectomy	[14]
Necchi *et al.* (2015)	28	Regional lymph nodes: $n=16$, metastatic nodal disease: $n=3$, lymph node or soft tissue relapse after surgery: $n=9$	CR (25%, 7/28), PR (60.7%, 17/28), SD (14.3%, 4/28)	pT0pN0 29% (8/28)	Median OS 37 months from the start of chemotherapy, 5-year OS 48.7% from the start of chemotherapy	[15▪]
Urakami *et al.* (2015)	51	Lymph nodes: $n=51$	CR (20%, 12/60), PR (55%, 33/60), SD (17%. 10/60), PD (8%, 5/60). Nine did not undergo surgery.	pT0pN0 14% (7/51)	Median OS 31.6 months from the start of chemotherapy, 5-year OS 42% from the start of chemotherapy	[16]

CR, complete response; DSS, disease- specific survival; IR, incomplete response; NC, no change; OS, overall survival; PR, partial response; SD, stable disease.
[a]Of 41, cystectomy completed in 24.

was the most beneficial in patients with CR after first-line systemic chemotherapy. From the Memorial Sloan-Kettering Cancer Center, Herr *et al.* [9] reported that of 207 locally advanced bladder cancer patients treated with a cisplatin-based combined regimen, 80 (39%) ultimately underwent postchemotherapy surgery. On pathological examination, no viable cells remained in 30% (24/80) of patients, and 58% (14/ 24) survived from 9 months to 5 years. Of the 49 patients who achieved surgical CR, 41% (20/49) survived. None of the patients without a major response to chemotherapy survived for 5 years after postchemotherapy surgery, and only one of the 12 patients who refused surgery after a major response to chemotherapy survived for 3 years. Their observations roughly showed that about one-third of patients become candidates for postchemotherapy surgery, and one-third of these patients could survive after surgery. Very recently, Meijer *et al.* [10] also reported similar outcomes whereby of 125 nonorgan-confined bladder cancer patients undergoing postchemotherapy surgery, pathological CR was observed in 26.3% of patients, with the 5-year overall survival rate being 54%. In addition, there were two interesting and contrasting data in terms of surgical consolidation. Yafi *et al.* [38] reported the outcomes of patients who had an aborted cystectomy due to unresectable bladder cancer. In their series, between 1993 and 2007, radical cystectomy was planned in 300 patients, and it was aborted in 31 patients due to fixed disease involving the pelvis and rectum or extensive and palpable lymph node disease. The outcome was dismal, and the 2 and 5-year overall survival rates were 41 and 0%, respectively. On the contrary, Herr and Donat [39] reported the treatment outcomes of grossly pelvic lymph node-positive bladder cancer patients. No patient underwent neoadjuvant or adjuvant chemotherapy, and 24% (20/84) survived after radical cystectomy alone. The median survival time was 19 months [95% confidence interval (CI) 12–26] for all patients and 10 years (range 3–14) for surviving patients.

Regarding the resection of nonregional lymph node metastases, several researchers have reported promising outcomes [11–16]. Sweeney *et al.* [11] reported the outcomes of their phase 2 study of a combined surgery and chemotherapy approach to sub-diaphragmatic lymph metastasis from bladder carcinoma in the absence of distant metastasis. A total of 11 patients with CR ($n=7$) or PR ($n=4$) after systemic chemotherapy were included. After postchemotherapy bilateral complete retroperitoneal lymph node dissection (seven underwent concurrent cystectomy), nine patients (82%, 9/11) had residual disease in the retroperitoneal nodes on pathological examination, and the 4-year disease-specific and recurrence-free survival rates were 36 and 27%. Sub-analysis revealed that the number of viable tumors in less than two lymph nodes was correlated with prolonged disease-specific ($P=0.006$), and recurrence-free ($P=0.01$) survival. de Vries *et al.* [13] reported their aggressive approach to sub-diaphragmatic lymph node metastasis from bladder carcinoma in the absence of distant metastasis. After four cycles of cisplatin-based chemotherapy, 14 patients (CR = 5, PR = 9) underwent complete retroperitoneal lymph node dissection and cystectomy. On pathological examination, no residual disease was detected in 29% (4/14) of patients, and the 3 and 5-year disease-specific survival rates were 36 and 24%, respectively. Very recently, Necchi *et al.* [15▪] also supported an aggressive surgical approach to this disease entity. Of 59 patients with sub-diaphragmatic, abdominal, or pelvic nodal disease and who showed at least stable disease after 4–6 cycles of a modified MVAC regimen (35 had metastasis at diagnosis, whereas 24 developed relapse after surgery), 28 underwent postchemotherapy consolidative surgery (study group, pelvic lymph node dissection: $n=14$, retroperitoneal lymph node dissection: $n=11$, both: $n=3$), whereas 31 did not (control group) due to either achieving CR after modified MVAC ($n=9$), undergoing consolidative chemotherapy with/ without radiation ($n=14$), a history of major complications after the previous surgery ($n=4$), or unknown reasons ($n=4$). On pathological examination, no viable cells remained in 29% (8/28) of patients of the study group. The median overall survival was 37 months in the study group, whereas it was 19 months in the control group (log-rank test, $P=0.005$). Postchemotherapy surgery remained significant in a multivariate model (hazard ratio 0.30, 95% CI 0.13–0.70, $P=0.005$).

RESECTION OF VISCERAL METASTASIS

As described above, since the first promising study by Cowles *et al.* [17], visceral metastasectomy has been offered to selected patients. Table 2 summarizes the outcomes of metastasectomy for visceral organs [18–28]. For example, Siefker-Radtke *et al.* [18] reported the outcomes of 31 metastatic urothelial carcinoma patients treated with metastasectomy between 1985 and 2001. The resected sites were the lung (77%, 24/31), distant lymph nodes (13%, 4/31), brain (7%, 2/31), and skin (3%, 1/31). The disease was completely resected in 30 patients. On pathological examination, viable cells were confirmed in 94% (29/31) of the specimens. The median survival time from metastasectomy was 23 months, and the

Table 2. Treatment outcomes of metastasectomy for visceral metastases

Study (year)	No. of patients	Resected sites	Chemotherapy responses	Pathology	Outcome	Reference
Metastasectomy including visceral organs other than lung						
Siefker-Radtke *et al.* (2004)	31	Lung: $n=24$, distant lymph nodes: $n=4$, brain: $n=2$, subcutaneous metastasis: $n=1$	Of the 31 patients, 22 received systemic chemotherapy before the metastasectomy. Of the nine patients undergoing surgery as initial treatment of metastases, four received adjuvant chemotherapy after resection. Responses were not assessed.	Viable cells were confirmed in 94% (29/31) of the specimens.	Median OS 23 months from metastasectomy, 5-year OS 33% from metastasectomy	[18]
Lenmann *et al.* (2009)	44	Lymph nodes: $n=30$, lung: $n=8$, bone: $n=2$, adrenal gland: $n=1$, brain: $n=1$, small intestine: $n=1$, subcutaneous metastasis: $n=1$	Thirty-five patients underwent systemic chemotherapy at some point. Of the 22 patients receiving systemic chemotherapy before metastasectomy, 4 (18%, 4/22) showed a complete response.	Of 22 patients undergoing systemic chemotherapy before metastasectomy, 18 patients (82%, 18/22) had viable cells.	Median OS 27 months from metastasectomy, 5-year OS 28% from metastasectomy	[19]
Abe *et al.* (2007)	12	Lung: $n=7$, lymph nodes: $n=3$, pelvic exenteration: $n=1$, local recurrence: $n=1$	Ten patients received systemic chemotherapy before metastasectomy. CR (10%, 1/10), PR (80%, 8/10), NC (10%, 1/10)	Viable cells were confirmed in 83% (10/12) of the specimens.	Median OS 42 months from the initiation of treatment	[20]
Abe *et al.* (2014)	42	Lymph nodes: $n=20$, lung: $n=12$, pelvic exenteration: $n=3$, local recurrence: $n=2$, subcutaneous metastasis: $n=2$, liver resection: $n=1$, others: $n=2$	All except one case received systemic chemotherapy. Metactasectomy after systemic chemotherapy was dominant ($n=34$). Responses were not assessed.	Viable cells were confirmed in 71% (30/42) of the specimens.	Median OS 26 months from metastasectomy, 5-year OS 31% from metastasectomy	[21]
Miller *et al.* (1993)	36[a]	Locally advanced (T4: $n=3$, local regional: $n=17$, metatstatic: $n=16$)	Patients without progressive disease after 4 cycles of the CMV regimen were considered eligible for surgery.	Viable cells were confirmed in 83% (25/36) of the specimens.	3-year OS 82% for pathological CR group, 46% for surgical CR group, and 0% for unresectable group from the start of chemotherapy.	[22]
Dodd *et al.* (1999)	50[b]	Initially unresectable primary tumor: $n=4$, lymph nodes or abdominal/pelvic mass: $n=32$, lung: $n=10$, bone: $n=3$, liver: $n=1$	CR (16%, 8/50), PR (66%, 33/50), NC (14%. 7/50), unknown (4%, 2/50)	Thirty-three patients (66%, 33/50) had viable cells at postchemotherapy surgery.	Five-year OS 33% from the start of chemotherapy in the 30 patients who attained surgical CR, and 41% from the start of chemotherapy in the 17 patients who attained pathological CR.	[23]
Nakagawa *et al.* (2013)	13	Lung: $n=8$, lymph nodes: $n=3$, ileal conduit and surrounding lymph nodes: $n=1$, brain: $n=1$	Premetastasectomy chemotherapy using a platinum agent was performed in 4 patients.	Pathology was not described.	Median OS 31.3 months after recurrence documented	[24]
Kim *et al.* (2015)	30	Lung: $n=24$, lymph nodes: $n=3$, liver: $n=2$, bone: $n=1$	Of the 30 patients, 28 underwent metastasectomy as the initial treatment, whereas 2 patients received systemic chemotherapy before the metastasectomy. Responses were not assessed.	Pathology was not described.	Median OS 30 months from metastasectomy, 3-year OS 41% from metastasectomy	[25]
Metastsectomy for lung metastatsis						
Kanzaki *et al.* (2010)	18	Lung: $n=18$	Eight (44%, 8/18) patients underwent systemic chemotherapy at some point. Responses were not assessed.	UC metastasis was confirmed in all resected specimens.	5-year OS 46.5% from metastasectomy	[26]
Matsuguma *et al.* (2011)	32	Lung: $n=32$	Sixteen (50%, 16/32) patients underwent systemic chemotherapy at some point. Responses were not assessed.	Pathology was not described.	5-year OS 50% from metastasectomy	[27]
Han *et al.* (2012)	16	Lung: $n=16$	Perioperative chemotherapy was done in 14 patients. Responses were not assessed.	Pathology was not described.	5-year OS 65.3% from metastasectomy	[28]

CMV, cisplatin, methotrexate and vinblastine; CR, complete response; NC, no change; OS, overall survival; PR, partial response.
[a]Eleven patients had unresectable disease.
[b]Three patients had unresectable disease.

5-year survival rate from metastasectomy was 33%. In a multi-institutional study involving 15 German uro-oncological centers, Lehmann *et al.* [19] reported the outcomes of 44 metastatic urothelial carcinoma patients who underwent metastasectomy between 1991 and 2008. Resected sites were the retroperitoneal lymph nodes (56.8%, 25/44), lung (18.2%, 8/44), distant lymph nodes (11.4%, 5/44), bone (4.5%, 2/44), adrenal gland (2.3%, 1/44), brain (2.3%, 1/44), small intestine (2.3%, 1/44), and skin (2.3%, 1/44). About 80% (35/44) of the patients received systemic chemotherapy before and/or after metastasectomy. Of 22 patients undergoing systemic chemotherapy before metastasectomy, 18 patients (82%, 18/22) had viable cells. The overall 5-year survival rate from metastasectomy was 28%, and seven patients without disease progression survived for more than 2 years and remained free from disease progression at a median follow-up of 63 months. Regarding prognostic factors, they did not identify any clinical characteristics associated with prolonged survival. Our group also collected data following treatment by metastasectomy for urothelial carcinoma patients in a multi-institutional study [21]. Between 1989 and 2012, 42 patients underwent metastasectomy with a curative intent at four Japanese university hospitals. Resected sites were the lymph nodes [47.6%, 20/42 (retroperitoneal lymph nodes below aortic bifurcation: $n=6$, retroperitoneal lymph nodes above aortic bifurcation: $n=9$, distant lymph nodes: $n=5$)], lung (28.6%, 12/42), pelvic exenteration (7.1%, 3/42), local recurrence (4.8%, 2/42), skin (4.8%, 2/42), liver (2.4%, 1/42), lower leg (2.4%, 1/42), and adrenal gland (2.4%, 1/42). Viable cells were confirmed in 71% (30/42) of the specimens. The median overall survival was 26 months from metastasectomy, and the 5-year overall survival rate after metastasectomy was 31%. In a univariate model, surgical consolidation for a solitary lung or solitary lymph node metastasis was associated with prolonged survival (81 vs. 19 months for the other patients, log-rank test $P=0.0296$).

Recently, several groups reported promising outcomes following surgical resection for pulmonary urothelial carcinoma metastasis [26–28]. Kanzaki *et al.* [26] reported outcomes whereby, in 18 patients undergoing pulmonary metastasectomy from urothelial carcinoma, the 3 and 5-year overall survival rates were 59.8 and 46.5% respectively. They also observed a 5-year overall survival rate of 85.7% in solitary metastatic patients and 20% in multiple metastatic patients. Matsuguma *et al.* [27] reviewed their experiences involving 32 patients undergoing pulmonary surgical resection. Of the 32 patients, 11 underwent video-assisted thoracic surgery (VATS). The 5-year overall survival rate was 50%, and a size smaller than 3 cm was associated with prolonged survival in a multivariate model. Kim *et al.* [25] also reported the outcomes in 30 patients with metastatic urothelial carcinoma treated by metastasectomy between 2000 and 2014. Resected sites were the lung (80%, 24/80), lymph nodes (10%, 3/30), liver (7%, 2/30), and bone (3%, 1/30). The median overall survival time was 30 months from the time of metastasectomy, with a 3-year survival rate of 41%. Multivariate analysis revealed that nonpulmonary metastasectomy was the only independent adverse factor of overall survival (hazard ratio 9.10, $P=0.001$). Subgroup analysis of the pulmonary resection group showed that patients with solitary lung metastasis had a significantly longer progression-free survival than those with two or more (68 vs. 7 months, respectively; $P<0.0019$). Recent accumulations of data regarding pulmonary resection for metastatic urothelial carcinoma reflect recent progress in endoscopic surgery, namely VATS in lung surgery, which could motivate patients and physicians to face the challenge of surgical elimination, if metastasis can be minimum-invasively resected. Recently, the feasibility of and improved postoperative convalescence following laparoscopic liver resection of colorectal metastases has been reported [40,41]. Although solitary liver metastasis is rare in metastatic urothelial carcinoma, laparoscopic surgery might become an alternative procedure. In the near future, T-cell checkpoint-targeting agents like programmed cell death protein 1 and programmed death-ligand 1 inhibitors may make marked progress to improve treatment outcomes for metastatic urothelial carcinoma patients [42]. Nevertheless, we consider that surgical consolidation will still remain in our armamentarium.

CONCLUSION

The role of metastasectomy in metastatic urothelial carcinoma has not yet been examined in a randomized setting. Each study group has offered surgical consolidation to metastatic urothelial carcinoma patients according to their own guidelines, and there are many things in common, such as a good response to systemic chemotherapy, limited disease, the feasibility of resection, and a favorable performance status. In terms of locally advanced and/or node-positive bladder cancer, further studies supported the benefit of surgical consolidation after a good response to systemic chemotherapy. Regarding metastasectomy for visceral metastasis, recent evidence suggested that lung metastases (ideally a

small solitary lesion) would be a good indication. Careful patient selection is mandatory.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. von der Maase H, Hansen SW, Roberts JT, *et al.* Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000; 18:3068–3077.
2. Sonpavde G, Pond GR, Choueiri TK, *et al.* Single-agent taxane versus taxane-containing combination chemotherapy as salvage therapy for advanced urothelial carcinoma. Eur Urol 2016; 69:634–641.
3. Shinohara N, Harabayashi T, Suzuki S, *et al.* Salvage chemotherapy with paclitaxel, ifosfamide, and nedaplatin in patients with urothelial cancer who had received prior cisplatin-based therapy. Cancer Chemother Pharmacol 2006; 58:402–407.
4. Kitamura H, Taguchi K, Kunishima Y, *et al.* Paclitaxel, ifosfamide, and nedaplatin as second-line treatment for patients with metastatic urothelial carcinoma: a phase II study of the SUOC group. Cancer Sci 2011; 102:1171–1175.
5. Sternberg CN, Calabro F, Pizzocaro G, *et al.* Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer 2001; 92:2993–2998.
6. Bellmunt J, Theodore C, Demkov T, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009; 27:4454–4461.
7. Medioni J, Di Palma M, Guillot A, *et al.* Efficacy and safety of Vinflunine for advanced or metastatic urothelial carcinoma in routine practice based on the French multicentre CURVE study. BMC Cancer 2016; 16:217.
8. Donat SM, Herr HW, Bajorin DF, *et al.* Methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy and cystectomy for unresectable bladder cancer. J Urol 1996; 156:368–371.
9. Herr HW, Donat SM, Bajorin DF. Postchemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. J Urol 2001; 165:811–814.
10. Meijer RP, Nieuwenhuijzen JA, Meinhardt W, *et al.* Response to induction chemotherapy and surgery in nonorgan confined bladder cancer: a single institution experience. Eur J Surg Oncol 2013; 39:365–371.
11. Sweeney P, Millikan R, Donat M, *et al.* Is there a therapeutic role for postchemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? J Urol 2003; 169:2113–2117.
12. Kim CJ, Wakabayashi Y, Kushima R, *et al.* Retroperitoneal lymph node dissection in patients with interaortocaval lymph node metastases of transitional cell carcinoma of the urinary tract. Int J Urol 2004; 11:243–247.
13. de Vries RR, Nieuwenhuijzen JA, Meinhardt W, *et al.* Long-term survival after combined modality treatment in metastatic bladder cancer patients presenting with supra-regional tumor positive lymph nodes only. Eur J Surg Oncol 2009; 35:352–355.
14. Childs MA, Wood CG, Spiess PE, *et al.* Early results of chemotherapy with retroperitoneal lymph node dissection for isolated retroperitoneal recurrence of upper urinary tract urothelial carcinoma after nephroureterectomy. Can J Urol 2010; 17:5184–5189.
15. ■ Necchi A, Giannatempo P, Lo Vullo S, *et al.* Postchemotherapy lymphadenectomy in patients with metastatic urothelial carcinoma: long-term efficacy and implications for trial design. Clin Genitourin Cancer 2015; 13:80–86; e81.

This is a retrospectove study from Italy that the authors compared the survivals between the patients undergoing postchemotherapy pelvic or retro-peritoneal lymphadenectomy and those without surgery.

16. Urakami S, Yuasa T, Yamamoto S, *et al.* Clinical response to induction chemotherapy predicts improved survival outcome in urothelial carcinoma with clinical lymph nodal metastasis treated by consolidative surgery. Int J Clin Oncol 2015; 20:1171–1178.
17. Cowles RS, Johnson DE, McMurtrey MJ. Long-term results following thoracotomy for metastatic bladder cancer. Urology 1982; 20:390–392.
18. Siefker-Radtke AO, Walsh GL, Pisters LL, *et al.* Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. J Urol 2004; 171:145–148.
19. Lehmann J, Suttmann H, Albers P, *et al.* Surgery for metastatic urothelial carcinoma with curative intent: the German experience (AUO AB 30/05). Eur Urol 2009; 55:1293–1299.
20. Abe T, Shinohara N, Harabayashi T, *et al.* Impact of multimodal treatment on survival in patients with metastatic urothelial cancer. Eur Urol 2007; 52:1106–1113.
21. Abe T, Kitamura H, Obara W, *et al.* Outcome of metastasectomy for urothelial carcinoma: a multiinstitutional retrospective study in Japan. J Urol 2014; 191:932–936.
22. Miller RS, Freiha FS, Reese JH, *et al.* Cisplatin, methotrexate and vinblastine plus surgical restaging for patients with advanced transitional cell carcinoma of the urothelium. J Urol 1993; 150:65–69.
23. Dodd PM, McCaffrey JA, Herr H, *et al.* Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. J Clin Oncol 1999; 17:2546–2552.
24. Nakagawa T, Hara T, Kawahara T, *et al.* Prognostic risk stratification of patients with urothelial carcinoma of the bladder with recurrence after radical cystectomy. J Urol 2013; 189:1275–1281.
25. Kim T, Ahn JH, You D, *et al.* Pulmonary metastasectomy could prolong overall survival in select cases of metastatic urinary tract cancer. Clin Genitourin Cancer 2015; 13:e297–e304.
26. Kanzaki R, Higashiyama M, Fujiwara A, *et al.* Outcome of surgical resection of pulmonary metastasis from urinary tract transitional cell carcinoma. Interact Cardiovasc Thorac Surg 2010; 11:60–64.
27. Matsuguma H, Yoshino I, Ito H, *et al.* Is there a role for pulmonary metastasectomy with a curative intent in patients with metastatic urinary transitional cell carcinoma? Ann Thorac Surg 2011; 92:449–453.
28. Han WS, Kim K, Park JS. Result of surgical resection for pulmonary metastasis from urothelial carcinoma. Korean J Thorac Cardiovasc Surg 2012; 45:242–245.
29. Herr HW. Is metastasectomy for urothelial carcinoma worthwhile? Eur Urol 2009; 55:1300–1301.
30. Oechsle K, Hartmann M, Brenner W, *et al.* [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. J Clin Oncol 2008; 26:5930–5935.
31. De Santis M, Becherer A, Bokemeyer C, *et al.* 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. J Clin Oncol 2004; 22:1034–1039.
32. Johns Putra L, Lawrentschuk N, Ballok Z, *et al.* 18F-fluorodeoxyglucose positron emission tomography in evaluation of germ cell tumor after chemotherapy. Urology 2004; 64:1202–1207.
33. Hinz S, Schrader M, Kempkensteffen C, *et al.* The role of positron emission tomography in the evaluation of residual masses after chemotherapy for advanced stage seminoma. J Urol 2008; 179:936–940; discussion 940.
34. Kitajima K, Yamamoto S, Fukushima K, *et al.* FDG-PET/CT as a posttreatment restaging tool in urothelial carcinoma: comparison with contrast-enhanced CT. Eur J Radiol 2016; 85:593–598.
35. Giannatempo P, Alessi A, Miceli R, *et al.* Interim fluorine-18 fluorodeoxyglucose positron emission tomography for early metabolic assessment of therapeutic response to chemotherapy for metastatic transitional cell carcinoma. Clin Genitourin Cancer 2014; 12:433–439.
36. Otto T, Krege S, Suhr J, *et al.* Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. Urology 2001; 57:55–59.
37. Dimopoulos MA, Finn L, Logothetis CJ. Pattern of failure and survival of patients with metastatic urothelial tumors relapsing after cis-platinum-based chemotherapy. J Urol 1994; 151:598–600. [discussion 600–591]
38. Yafi FA, Duclos M, Correa JA, *et al.* Contemporary outcome and management of patients who had an aborted cystectomy due to unresectable bladder cancer. Urol Oncol 2011; 29:309–313.
39. Herr HW, Donat SM. Outcome of patients with grossly node positive bladder cancer after pelvic lymph node dissection and radical cystectomy. J Urol 2001; 165:62–64. [discussion 64]
40. Schiffman SC, Kim KH, Tsung A, *et al.* Laparoscopic versus open liver resection for metastatic colorectal cancer: a metaanalysis of 610 patients. Surgery 2015; 157:211–222.
41. Kazaryan AM, Marangos IP, Rosok BI, *et al.* Laparoscopic resection of colorectal liver metastases: surgical and long-term oncologic outcome. Ann Surg 2010; 252:1005–1012.
42. Powles T, Eder JP, Fine GD, *et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014; 515:558–562.