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Long-term survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for patients with peritoneal metastases of urachal cancer

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ABSTRACT

Introduction: Urachal adenocarcinoma (UrAC) is a rare malignancy arising from persistent urachal remnants, which can cause peritoneal metastases (PM). Currently, patients with this stage UrAC are considered beyond cure. Our objective is to report long-term oncological outcome after cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for patients with PM of urachal adenocarcinoma (UrAC).

Materials and methods: We identified 55 patients with UrAC treated at our hospital between 1994 and 2017. Patients were staged with CT, bone scintigraphy and/or PET/CT. From 2001 on, cN0M0 patients underwent staging laparoscopy. Ten patients had PM and were treated with CRS/HIPEC; 35 showed no metastases and underwent local treatment; 10 had distant metastases and received palliative chemotherapy.

Disease-specific survival (DSS) rates were estimated using the Kaplan-Meier method and log-rank tests. Postoperative complications represent a secondary outcome.

Results: The median follow-up was 96.8 months. Of the CRS/HIPEC patients, 5 (50%) developed a recurrence; 4 (40%) died of disease. The 2-yr and 5-yr DSS after CRS/HIPEC were 66.7% and 55.6%, respectively. DSS of the CRS/HIPEC patients did not significantly differ from DSS of patients without metastases who only underwent curative local treatment and was superior to patients with distant metastases ($P = 0.012$). The overall complication rate after CRS/HIPEC was 60%. Major complications (Clavien 3) constituted 20%. The study is limited by its retrospective nature and the small sample size.

Conclusion: CRS/HIPEC demonstrates satisfactory long-term oncological outcome for patients with PM of UrAC. It may be offered as a potentially curative treatment option for this group of patients.

Introduction

Urachal cancer is a rare malignancy arising from persistent urachal remnants, that are located at the bladder dome or between the bladder dome and the umbilicus. It accounts for <0.5% of

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bladder cancers [1,2]. Most of the urachal cancers are urachal adenocarcinomas (UrAC). Patients with urachal adenocarcinoma (UrAC) often present with mucinous disease, which most commonly metastasizes to liver, lungs, and bone, and may also disseminate to the peritoneal cavity, causing peritoneal metastases (PM) [3,4]. Evidence supporting curative treatment of this aggressive presentation is lacking. As a consequence, patients with metastasized UrAC have a dismal prognosis with a median survival of 1.3 years after systemic palliative chemotherapy [5,6].

Histologically, UrAC resembles enteric adenocarcinoma, rather than urothelial cancer of the bladder. Consequently, UrAC is more likely to respond to the kind of chemotherapy that is used to treat enteric cancers [7,8]. The options for management of enteric cancers have been expanded by the use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with limited PM. Multiple phase 2 and 3 trials have shown improved survival in comparison with systemic chemotherapy [9–11]. Therefore, CRS/HIPEC has been adopted as the new standard of care for pseudomyxoma peritonei and for selected patients with PM of colorectal cancer and appendiceal cancer [12,13].

Given the histological similarities between UrAC and enteric adenocarcinomas, CRS/HIPEC has been hypothesized to be a treatment option for PM of UrAC and has been performed in a very limited number of patients [14,15]. The present study is the first reporting (long-term) oncological outcome after CRS/HIPEC for PM of UrAC.

Materials and methods

Patients

We studied a total of 55 consecutive patients with UrAC who presented at The Netherlands Cancer Institute between January 1994 and January 2017. All patients were referred to our tertiary oncology hospital, after initial biopsy showing adenocarcinoma of the bladder dome or imaging findings suspicious for urachal cancer. Analyses were retrospectively performed from a prospectively maintained institutional genitourinary-cancer database. The study was carried out in accordance with institutional ethical guidelines, based on Good Clinical Practice.

Staging

Initial staging consisted of physical examination, cystoscopy, CT-scan of the abdomen, pelvis and chest (with intravenous and oral contrast) and bone scintigraphy (before 2011) or a PET/CT (after 2011). The transurethral resection specimens were collected and reviewed by a dedicated uropathologist (JdJ), confirming urachal adenocarcinoma. Patients were staged according to the Sheldon staging system [2]. Starting in 2001, a diagnostic supra-umbilical laparoscopy with abdominal cytology (and biopsy of any suspicious lesions) was added as part of the staging algorithm in cN0M0 patients with a mucinous tumor.

Treatment

Patients were discussed at multidisciplinary rounds to decide on definitive treatment. In general, patients with no metastases on imaging and no suspicion of PM received local treatment, as detailed below. Patients in whom PM were detected, were considered for CRS/HIPEC if there were no systemic metastases and if a complete cytoreduction was considered feasible. Patients with distant metastases on imaging were considered for palliative care (palliative chemotherapy and – in case of symptomatic bone metastases – palliative radiotherapy).

Local treatment

Local treatment consisted of external beam radiotherapy followed by surgical resection. Preoperatively, 20×2 Gy external-beam radiation was administered. Subsequently, a partial cystectomy with en-bloc resection of the umbilicus (excision of a strip of peritoneum, posterior rectus sheath, umbilicus and bladder dome) was performed. Intra-operative brachytherapy to the suture line of the bladder was added. Adjuvant chemotherapy was not routinely offered. Chemotherapy regimens corresponded to those used for colorectal adenocarcinoma (initially a combination of 5-fluoro-uracil, leucovorin and, since 2004, oxaliplatin or capecitabin and oxaliplatin during 6 months.

CRS/HIPEC

In patients with PM proven by abdominal cytology and/or biopsy, resection was performed, as described above. Thereafter, while leaving the bladder open, CRS was performed by systematically inspecting the abdominal cavity. The extent of peritoneal disease was assessed using the peritoneal cancer index (PCI: a numeric score from 0 to 39, based on the distribution and size of cancerous lesions) [17].

The aim of CRS was to achieve a complete cytoreduction (removal of all macroscopic tumor). This was achieved by a combination of visceral resections and peritonectomy procedures. Routinely, a radical greater omentectomy was performed and, in postmenopausal female patients, a bilateral salpingo-oophorectomy. The completeness of cytoreduction was scored using the CC-score: CC0 indicating no visible tumor remnants, CC1 tumor nodules <0.25 cm, CC2 tumor nodules 0.25–2.5 cm and CC3 tumor nodules >2.5 cm [17].

After CRS, HIPEC was performed using the open coliseum technique [18]. This technique is performed with an open bladder and three inflow catheters situated in the bladder, in the upper abdomen and in the lower abdomen. Two outflow catheters are placed in the midline of the abdomen. After 90 min of perfusion with Mitomycin C 35 mg/m^2 at 42° Celsius (in Dianeal), the abdomen was drained, washed and brachytherapy to the suture line of the bladder was performed after closure of the bladder. Two abdominal drains were kept for five days postoperatively. Six months adjuvant chemotherapy was offered. In one patient, CRS/HIPEC was combined with cystoprostatectomy, pelvic lymph node dissection and urinary diversion (Bricker) because concomitant adenocarcinoma of the prostate was found (pT3aN1(1/39)MxR0, Gleason-score $4 + 3 = 7$, iPSA 26.9) at time of UrAC diagnosis.

Follow up

The median follow-up of the study was 96.8 months (interquartile range (IQR): 38.2–121.5 months), measured using the reversed Kaplan Meier method. Follow-up was conducted using a standard follow-up scheme which included physical examination, cystoscopy, laboratory test (CEA tumor-marker, alkaline phosphatase) and CT imaging every 3 months during the initial 2 years, and then every 6 months. Follow-up was ended when the patient died or usually after 10 years without recurrence. Postoperative complications were recorded in accordance to the Clavien-Dindo classification of surgical complications [19].

Statistics

Differences in patient characteristics of the palliative group, the local treatment group and the CRS/HIPEC (PM) group were evaluated using the Pearson chi-square and Fisher exact tests. Disease

specific survival (DSS) was analyzed using the Kaplan Meier method. DSS of the CRS/HIPEC group was compared with DSS of patients undergoing local treatment only and palliative treatment (log-rank tests). All reported P values are 2-sided, with significance set at $P < 0.05$. Data were analyzed with SPSS, version 22.

Results

Patients

A total of 55 patients (median age: 55 years; IQR 47–62 years) with UrAC were treated at our hospital. Fig. 1 displays the distribution of these patients among the three treatment groups. In summary, 10 underwent CRS/HIPEC because of limited PM of UrAC; 35 underwent local treatment because of cN0M0 UrAC; and 10 received palliative treatment because of metastasized UrAC. Table 1 shows the corresponding patient and tumor characteristics. Of the patients with PM, all were mucinous tumors; one showed signet-ring cell histology, two mixed type.

Peritoneal metastases

All patients treated with CRS/HIPEC for limited PM were staged cN0M0. Based on staging laparoscopy after 2001, 7 patients were found to have PC and were selected for CRS/HIPEC. The other 3 were identified during the local surgery (before 2001). The median peritoneal cancer index (PCI) was 6 (range 2–11). In 7/10 (70.0%) patients CC-0 or CC-1 cytoreduction was achieved.

CRS/HIPEC survival

Five patients (50.0%) developed a recurrence after CRS/HIPEC after a median period of 8 months (range: 4–22 months). Four of these patients received palliative chemotherapy for metastatic disease; the fifth underwent a second curative HIPEC procedure and was free of disease at last follow-up. Four patients (40.0%) died of disease, after a median period of 21 months (range: 16–41 months). The estimated 2-year and 5-year DSS rates were 66.7% (95% CI: 33%–90%) and 55.6% (24%–84%), respectively. Median DSS was not reached. Neither a statistically significant difference was found between patients in whom a CC-0 or CC-1 was achieved, versus a CC-2 or CC-3 ($P = 0.239$), nor between patients with a CC-0 versus CC-1/2/3 ($P = 0.266$).

Survival comparison

Thirty-five patients only received local treatment for cN0M0 UrAC. Seventeen developed a recurrence after a median period of 13 months (range: 1–172 months). Twelve died of disease during follow-up after a median period of 30 months (range: 11–49 months). The estimated 2-year and 5-year DSS rates were 88.0% (95% CI: 0.72–0.96) and 57.5% (95% CI 0.40–0.74), respectively. Median DSS was not reached. We found no difference in DSS between the local treatment group and the CRS/HIPEC cohort ($P = 0.859$).

Ten patients had distant metastases and received palliative chemotherapy. They all died during follow up. The estimated 2-year and 5-year DSS probability were 40% (95% CI: 0.14–0.73) and 20% (95% CI: 0.04–0.56), respectively. The median DSS was 10 months (95% CI: 3.7–16.3 months). The difference in DSS between the CRS/HIPEC group versus the palliative treatment group was statistically significant ($P = 0.012$).

In Fig. 2, the DSS after CRS/HIPEC is compared with DSS of the palliative group and the local treatment group ($P < 0.001$).

Postoperative complications

Postoperative complications after CRS/HIPEC occurred in 6/10 (60%) patients. Two patients had a Clavien Dindo grade 3 complication (20%): one had bladder leakage and needed bilateral percutaneous nephrostomies; the other had an infected lymphocele, which needed surgical drainage and intravenous antibiotic therapy. Grade 4 complications did not occur.

Discussion

The present study was carried out to report long-term oncological outcome after CRS/HIPEC for PM of UrAC. We found that more than half of the patients with PM treated with CRS/HIPEC remained recurrence-free and were still alive five years after the procedure. This demonstrates that long-term survival can be achieved with CRS/HIPEC for selected patients with PM of UrAC.

Whereas patients with non-metastasized UrAC are potentially curatively treated with a local resection of the tumor, patients with metastases traditionally receive palliative chemotherapy. This includes patients with PM, as, currently, surgical debulking procedures of metastatic UrAC are not recommended [6]. The present study shows a significant benefit in DSS for patients with PM versus patients with distant metastases. More importantly, DSS of patients with PM treated with CRS/HIPEC was comparable with DSS of patients without metastases. This indicates that PM should not always be viewed as diffuse metastatic cancer, but rather as advanced locoregional disease which can potentially curatively be treated with CRS/HIPEC.

To our knowledge, this study is the first report investigating survival of a consecutive cohort of UrAC patients including long-term follow-up. Previous reports already suggested a potential role for CRS/HIPEC in UrAC [14–16] but did not compare clinical outcome of CRS/HIPEC to other treatments like local excision or palliative treatment. Liu et al. [14] performed CRS/HIPEC in nine patients with PM arising from the urachus. Only one recurrence occurred and the median survival was 27.5 (range 6–61) months. On the other hand, Krane et al. [15] treated five patients with PM of UrAC with CRS/HIPEC, all of whom died of their disease after median 27 months. Mercier et al. [16] described 36 UrAC patients who were treated with CRS/HIPEC and reported that complete CRS in patients with limited PM was the key to long term survival. Taken together, clinical results of the 3 referenced studies were not compared with patients who had local excision only or patients who presented with organ metastases. Based on our long-term follow-up and comparison of CRS/HIPEC to local excision only, we believe that CRS/HIPEC is a curative option for patients with PM of UrAC.

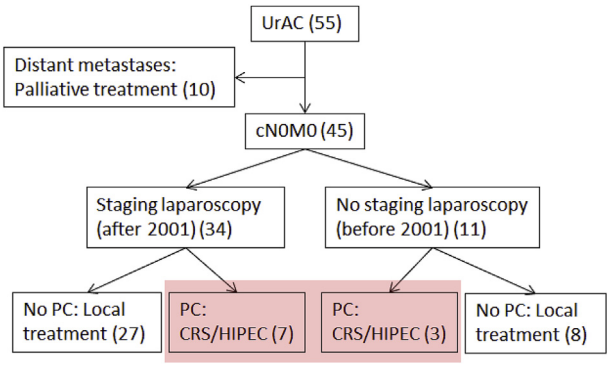

Fig. 1. Consort diagram of our patient cohort.

Table 1
Distribution of patients among the treatment groups
Patient and tumor characteristics for the three groups: CRS/HIPEC for patients with PC; local treatment for patients without metastases (cN0M0); palliative chemotherapy for patients with distant metastases of UrAC.

		CRS/HIPEC (N = 10)	Local treatment (N = 35)	Palliative treatment (N = 10)
Mean age in years (SD)		49.4 (15.3)	51.6 (10.4)	50.5 (9.8)
Gender	Male (%)	9 (90)	24 (68.6)	8 (80)
Mean tumor size in cm. (SD)		6.8 (3.4)	4.0 (2.2)	3.5 (1.4)
Sheldon stage	I/II (%)	0	11 (31.4)	0
	III/IV (%)	10 (100)	24 (68.6)	10 (100)
Mucinous histology (%)		10 (100)	29 (82.9)	10 (100)

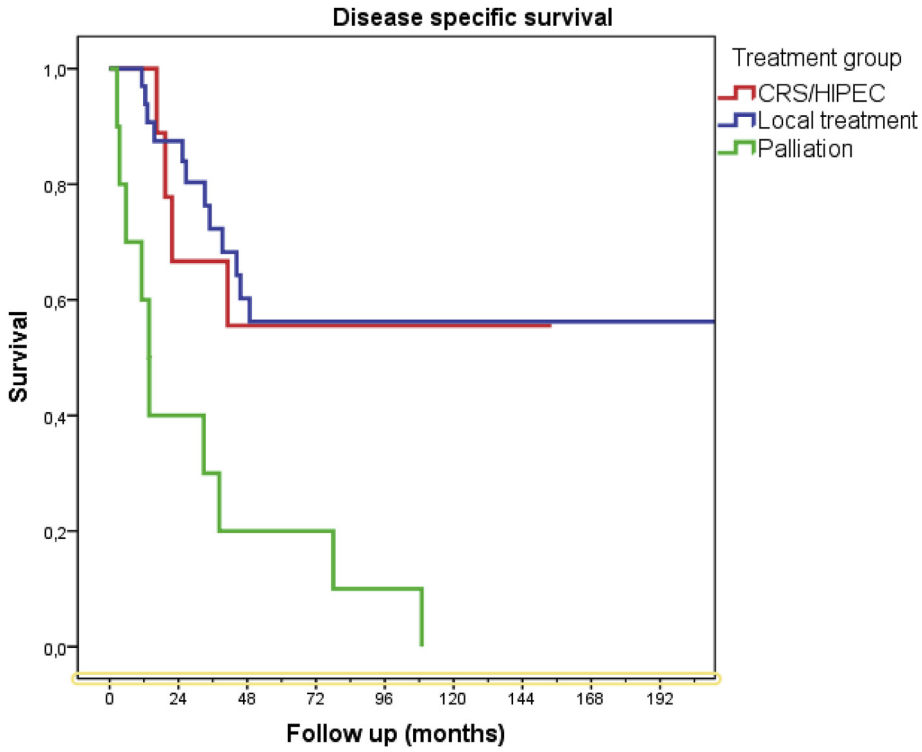

Fig. 2. Disease specific survival after CRS/HIPEC versus local treatment versus palliative treatment.

For other (enteric) adenocarcinomas, CRS/HIPEC has become the standard of care for well selected patients with limited PM. Multiple phase II and III trials showed improved survival in comparison with systemic chemotherapy [9–13]. The effectiveness of CRS/HIPEC in these malignancies highly depends on the extent of disease: if complete cytoreduction of PM could be obtained, 5-year survival rates of 45%–51% were achieved in combination with HIPEC, but survival was found to be significantly lower if not all visible tumor could be resected [20,21]. The 56% 5-year DSS in our study seems in line with these numbers. However, we did not find a significant difference in DSS between complete versus incomplete cytoreduction. This discrepancy might be explained by the very low number of patients and/or the relatively low PCI in our cohort. Nevertheless, the goal of CRS should be to achieve resection of all macroscopic disease.

This underscores the importance of carefully evaluating the extent and resectability of peritoneal disease before treatment. While CT is the most commonly used non-invasive method to detect metastases [22], it has been shown to have a sensitivity of only 11% for the detection of small PM (<0.5 cm). Hence, a significant underestimation of the extent of PC is evident [23], leaving many PM undetected until after the time of local surgery. We observed this in our series as well (before 2001). For this reason, staging laparoscopy was added to our staging algorithm in 2001, in order to detect and assess PC before definitive treatment.

The second objective of our study was to report post-operative complications after CRS/HIPEC. CRS/HIPEC is known to be associated with substantial morbidity leading to up to 65% grade ≥3 complications in other malignancies [24]. In contrast, we only found grade 3 complications in 20%. This difference may be explained by the fact that our patients rarely needed bowel resection(s) or anastomoses. Another possible explanation is the low PCI in our study. Our median PCI was 6, whereas a PCI >20 has been shown to be an important risk factor for postoperative complications [24]. Nevertheless, compared with other CRS/HIPEC studies, the complication rate of CRS/HIPEC for limited PM of UrAC seems acceptable.

The conclusions of our study should be interpreted within the context of its limitations. The first is the small sample-size, which impedes drawing definite conclusions. An example of this was the absence of a difference in DSS for patients who did and did not achieve complete CRS, ie. CC0 versus CC1/2/3/. As a national referral center, we treated 55 UrAC patients in 22 years, of whom 10 underwent CRS/HIPEC. This illustrates the rarity of UrAC, posing

significant challenges to clinical UrAC studies. Inherent to this rarity, the treatment strategies in our study were all empiric and institution-based. In addition to resection, local treatment consisted of pre-operative radiotherapy and brachytherapy to the suture lines. This was done because of the importance of the surgical margin status [2,4,25], but is not recommended by any universal guideline. Nor is the use of adjuvant chemotherapy advised in high-risk cases. Our treatment strategies and subsequent outcome might, therefore, differ from treatment strategies in other hospitals.

Finally, we acknowledge the retrospective observational study design. We did not aim to compare three different treatment strategies among comparable groups of patients (we treated patients without metastases versus patients with PC only versus patients with distant metastases). In that light, a survival difference between patients with PC who receive CRS/HIPEC and patients with metastatic spread to distant solid organs who receive palliation might not be surprising. However, taking into account these differences, the comparable survival plots for patients without organ-metastases are all the more remarkable.

Conclusions

In this cohort, CRS/HIPEC demonstrates satisfactory long-term oncological outcome with acceptable toxicity for patients with PM of UrAC. Notwithstanding the aforementioned limitations, CRS/HIPEC may be offered as a potentially curative treatment option for this group of patients instead of palliative chemotherapy alone. In the meanwhile, multi-center international collaborations might aid to further elucidate this and advance the care of patients with this rare malignancy.

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