Original Paper



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Simultaneous Cystectomy and Nephroureterectomy due to Synchronous Upper Urinary Tract Tumors and Invasive Bladder Cancer: Open and Laparoscopic Approaches

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Key Words

Transitional cell carcinoma • Upper urinary tract tumor • Cystectomy • Nephroureterectomy

Abstract

Introduction: It is not unusual for bladder tumors to appear following transitional cell carcinoma of the upper urinary tract (UUT), with involvement of the UUT, following invasive bladder cancer, being less common. The synchronous presence of transitional cell carcinoma of the bladder and of the UTT is exceptional. Methods: Fifteen simultaneous cystectomies with nephroureterectomies were performed due to synchronous UUT and invasive bladder cancers (1997–2009). Surgery was performed using an open approach in 10 patients, while the last 5 procedures were performed laparoscopically. Results: The mean age was 68.7 years. Mean surgery time was 348.6 minutes. Mean blood loss was 816 ml. Acute renal failure was the most frequent postoperative complication being present in 5 patients (33%). There was 1 case of a leak in the ureter-intestinal anastomosis (open approach), which required placement of a left-sided percutaneous nephrostomy. There were 2 cases of postoperative mortality, both in the open approach series and with intestinal neobladder. Mean follow-up time for the whole series was 21.25 months. Eight cases experienced metastatic progression of the disease (mean follow-up 17 months). Conclusion: Though multi-site studies with longer follow-up

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Accessible online at: www.karger.com/cur and a greater numbers of patients are needed, the moment at which urothelial tumors appear seems to influence their prognosis, with lower survival rates for tumors that synchronically appear. Copyright © 2012 S. Karger AG, Basel

Introduction

Transitional cell carcinoma (TCC) of the bladder is the sixth most frequent malignant tumor in the United States, representing 10% of cancers in men and 4% in women. Every year 67,160 new cases are diagnosed in the USA, with 13,750 deaths annually [1]. TCC of the upper urinary tract (UUT) is far less common than in the bladder, representing 5% of all urothelial neoplasms [2]. It is not unusual for bladder tumors to appear following TCC of the UUT (up to 50%) [3], with involvement of the UUT following invasive bladder cancer being less common (2-8%) [3-6]. This reflects in part the high mortality associated with invasive bladder TCC. The synchronous presence of TCC of the bladder and of the UUT is exceptional, with few studies describing its presence [7–11], and the majority of these cases being superficial bladder tumors.

We present our series in University Hospital La Paz of 15 cases of synchronous UTT tumor and invasive bladder cancer treated with simultaneous cystectomy

Manuel Pérez-Utrilla Pérez Hospital General Universitario Ciudad Real, Servicio Urología c/ Obispo Rafael Torija SN ES–13005 Ciudad Real (Spain) Tel. +34 926278000, E-Mail manuelperez_utrilla@hotmail.com and nephroureterectomy, 5 of which used a laparoscopic approach. To our knowledge, this is the most extensive series published in international literature to date.

Materials and Methods

From February 1997 to June 2009, 15 cystectomies with nephroureterectomies were performed due to synchronous UUT and invasive bladder cancers (table 1). Surgery was performed using an open approach in 10 patients (February 1997 to June 2003), while the last 5 procedures (from March 2005 to June 2009) were performed laparoscopically. Partial cystectomy was performed in 4 of the 10 open procedures for tumors located in the bladder dome/lateral wall that did not reveal carcinoma in situ on evaluation of the bladder. In all of the laparoscopic cases, reconstruction of the intestinal tract was performed via an infra-umbilical minilaparotomy and in 4 of these, urinary diversion was performed completely laparoscopically. There were no cases of conversion to open surgery. Our technique for laparoscopic nephroureterectomy and cystectomy was previously reported [12], in this case highlighting the use of a maximum of 6 or 7 trocars in each procedure (4 trocars for the nephroureterectomy, adding 2 or 3 for the cystectomy and lymph node dissection according to each patient's anthropometric characteristics). In all cases, the specimen was removed through infra-umbilical mini-laparotomy.

Systematic retroperitoneal lymph node dissection was not performed in either the open or the laparoscopic approach, and only in those cases in which lymph node involvement was suspected on imaging studies or intraoperatively. Routine pelvic lymph node dissection was performed in all cases.

Analysis was performed in August 2009 by retrospective review of the 15 patients.

Results

Table 1 describes the clinical characteristics of the entire series; a total of 12 men and 3 women. The mean age was 68.7 years (range 55–77 years). The mean surgery time for the series was 348.6 minutes (314 minutes in open surgery and 418 minutes laparoscopically). Mean blood loss was 816 ml. Average admission time was 17.8 days (range 8–45 days). Urine cytology was positive in 7 cases.

In terms of postoperative complications, there were no incidents in cases 1, 2, 5, 12 and 15, with a mean admission time for this group of 9.2 days. Four cases experienced paralytic ileus (cases 3, 7, 9 and 14). The complications were resolved in all cases using conservative measures that did not require re-intervention. Acute renal failure was the most frequent postoperative complication (33%), being present in 5 patients (cases 3, 8, 11, 13 and 14). Three of them reached normal measurement of creatinine after hydroelectrolytic reposition. Blood transfusion was necessary in 3 patients due to postoperative anemia, without the need for a second transfusion or re-intervention in any of these cases. There was 1 case of urine leak in the ureter-intestinal anastomosis (case 6), which required placement of a left-sided percutaneous nephrostomy. Case 4 was admitted to the intensive care unit on the 21st postoperative day due to distributive shock. The patient underwent surgical intervention the following day, revealing suture dehiscence in the intestinal neobladder, with subsequent good progress until day 32, when the patient required intubation and mechanical ventilation due to septic shock and respiratory distress. The blood cultures were positive for Aspergillus, Candida Albicans and Acinetobacter. The patient suffered acute renal failure, coagulopathy and multi-organ failure that resulted in death on the 45th postoperative day. Case 10 was admitted to the intensive care unit on the 10th postoperative day due to hyponatremia and gastrointestinal bleeding. Endoscopy was performed, revealing grade 3 esophageal varices and a bleeding ulcer in the pyloric antrum. The patient later suffered liver failure, hepatorenal syndrome, coagulopathy and metabolic encephalopathy, with multi-organ failure and death on the 21st postoperative day.

Table 2 shows histopathological characteristics, chemotherapy treatment and oncological follow-up. Eight deaths were recorded -2 postoperatively and 6 in follow-up. Excluding the 2 cases of postoperative death and 1 case in which follow-up was lost at 5 months, mean follow-up time for the whole series was 21.25 months.

No metastases were seen during follow-up of 5 cases (38%), with an average follow-up of 24.8 months. Of these, 4 received adjuvant chemotherapy -2 with gemcitabine + carboplatin and 2 with methotrexate, vinblastine, epirubicin and cisplatin (MVAC). Two local recurrences were diagnosed. One following nephroureterectomy + colpectomy + partial cystectomy due to myxoid leiomyosarcoma in the bladder with pericystic, vaginal dome and periureteral infiltration (recurrence of hysterectomy with double adnexectomy + adjuvant radiation therapy 6 years earlier). This patient showed bladder and intestinal recurrence at 1 year, was treated with total bladder resection and diverting colostomy. Followup was lost at 24 months. The other case showed urethral recurrence at 14 months following nephroureterectomy + radical cystectomy with negative borders (TCC pT4 of the renal pelvis and TCC pT4 of the bladder with carcinoma in situ). It was treated with urethrectomy and 4 months later the patient was diagnosed with liver metas-

Table 1. Patient characteristics

No.	Age	History of TURB	Symptom	Surgical technique	Blood transfusion, ml	Time,min	Stay, c
1	77	no	abdominal pain	right NU + right SR + partial cystectomy – retroperitoneal lymph node resection and PLND	350	230	9
2	72	no	lumbar pain	right NU + radical cystectomy + cutaneous ureterosigmoid- ostomy + PLND	800 – 2U PRBC	345	8
3	76	no	hematuria	left NU + partial cystectomy + PLND	1000 – 3U PRBC	345	21
4	69	yes: T1m G2	lumbar pain	left NU + radical cystectomy + lateral aortic lymph node dissection and PLND – ileo- cecal neobladder	500	315	45
5	77	no	lumbar pain	right NU + partial cystectomy + PLND	500	225	11
6	55	no	hematuria	right NU + radical cystectomy + retroperitoneal lymph node dissection and PLND + BWII	800 – 2U PRBC	360	23
7	72	no	hematuria	right NU + radical cystectomy + lateral peritoneal lymph node dissection and PLND +	500	290	16
8 9	60 73	yes: recurring Ta-1G3 no	hematuria lumbar pain	left ureterosigmoidostomy left NU + radical cystectomy + paraaortic lymph node dis- section and PLND + BWII	1600 – 5U PRBC 400	335 215	10 15
10	62	no	hematuria	left NU + partial cystectomy + PLND	2500 – 8U PRBC + 2UP	480	21
11	63	yes: recurring T1G3	pollakiuria	left NU + radical cystectomy + MOD. CAMEY II ortho- topic substitution enterocys- toplasty + paraaortic lymph node dissection and PLND	650	325	22
12	66	no	hematuria	lap. left NU + LRC + Lap PLND + right ureter-Bricker ileal conduit EEA	700 – 2U PRBC	470	10
13	63	no	hematuria	lap. left NU + LRC + lap. PLND + lap. BWII	1000 – 3U PRBC	600	22
14	74	no	hematuria	right lap. NU + LRC + Camey II neobladder + lap. left ureter reimplantation + lap. PLND	450	350	27
15	72	yes: T1m G2	hematuria	lap. right NU + LRC + lap. PLND + lap. BWII lap. left NU + LRC + lap. PLND + lap. BWII	500	345	8

EEA = End-to-end anastomosis; BWII = type II Bricker-Wallace; PRBC = packed red blood cells; LRC = laparoscopic radical cystectomy; <math>PLND = pelvic lymph node resection; Lap. = laparoscopic; NU = nephroureterectomy; SR = suprarenalectomy; TURB = transurethral resection of bladder; UP = units of plasma.

tases. The patient underwent chemotherapy and died due to progression of the disease 22 months after surgery.

Eight cases experienced metastatic progression of the disease; 4 of which had received adjuvant chemotherapy

(3 MVAC and 1 gemcitabine + carboplatin), 1 had received pelvic radiation therapy and the remaining three were without adjuvant treatment. Mean follow-up was 17 months and the mean time to diagnosis was 13.8 months.

Case	H.P. Cystectomy	H.P. Nephroureterectomy	CT-cycles	Mets- month	Follow-up
1 2	pT1G2pN0M0 urothelial pT3aG3pN0M0 + urothe- lial CIS + prostate pT2b- G2pN0M0 + urethra CIS	pT4G3pN2M0 urothelial pT1G2pNxM0 + urothelial CIS	MVEC 3 cycles MVEC 3 cycles	lung 1 month/liver 5 months no	5 months 8 months
3	pT2G3pN0M1 urothelial	pT1G2pNxM1 + urothelial CIS	no	lung 1 month/liver 4 months	5 months
4	Squamous metaplasia prostate PIN	chronic interstitial nephri- tis	NA	NA	NA
5	pT2G2pN0M0 urothelial	urothelial pT3bG3pNxM0	pelvic RT	lung/med 20 months	20 months
6	urothelial pT4aG3pN2M0, "nest type"	urothelial pT3bG3pN2M0	CMV 6 cycles	bone 6 months/liver 7 months	17 months
7	pT4aG3pN2M0 + urothe- lial CIS	urothelial pT4G3pN0M0	MVEC 3 cycles	liver 18 months	22 months
8	urothelial pT3bG3pN0M0 + prostate pT2bG2pN0M0	epidermoid pT3G3pN0M0 (renal pelvis) + urothelial pT1G3pN0M0 (ureter)	CMV 6 cycles	no	44 months
9	myxoid leiomyosarcoma pT4G3pN0M0	myxoid leiomyosarcoma pT3G3pNxM0	no	no; local bladder recurrence	24 months
10	urothelial pT3aG3pN0M0	urothelial pT1G2pN1M0	NA	NA	NA
11	pT3aG3pN0M0 + urothe- lial CIS	pT3G3pNxM0 + urothelial CIS, areas of squamous differentiation	Gemcit + Cbpt 5 cycles	no	8 months
12	urothelial pT3aG3pN0M0 + prostate PIN	renal granular cells eosino- phils pT3aG3pNxM0	Gemcit +Cispt 2 cycles	no	40 months
13	pT1G3pN0M0 + urothelial CIS + prostate pT2apN0M0	renal clear cells pT1aG2- pNxM0	no	lung 23 months	34 months
14	pT3apN2M0 + urothelial CISm -epidermoid (35%)	pT3G3pNxM0 + urothelial CIS – squamous	Gemcit + Cbpt 4 cycles	lung 24 months	25 months
15	bladder pT0 + prostate pT2G2pN0M0	urothelial pT1G2pNxM0 (pelvis and ureter)	no	lung and liver 4 months	8 months

 Table 2. Histopathological characteristics, chemotherapy treatment and oncological follow-up

Cbpt = Carboplatin; Cispt = cisplatin; CMV = cisplatin, methotrexate and vinblastine; Gemcit = Gemcitabine; Liv = Liver; Med = mediastinum; MVEC = methotrexate, vinblastine, epirubicin and cisplatin; NA= no applicable.

Four patients were not candidates for treatment, with 2 dying within a period of 1 month, follow-up being lost for the third (5 months) and the fourth, with a right perihilar mass and superior vena cava syndrome, and died 4 months after diagnosis. Four patients were candidates for treatment, and 1 of them is awaiting surgery for a pulmonary nodule. The 3 remaining patients were treated with chemotherapy; 2 with adriamycin, cyclophosphamide and cisplatin, with 1 dying at 4 months and the other requiring a second round of gemcitabine + paclitaxel (6 cycles) due to persistence of hepatic lesions, finally dying 10 months after diagnosis; the third with gemcitabine + carboplatin (6 cycles) with a follow-up of 11 months after diagnosis (partial remission).

Discussion

A distinguishing feature of the biological behaviour of urothelial TCCs is their multiple foci, causing them to appear synchronously or sequentially over the course of the urinary tract. There is scant literature reporting the synchronous presence of UUT cancer and invasive bladder TCC. Holton et al. [11] reported 9 cases of complete urinary tract extirpation (CUTE: bilateral nephroureterectomy, cystectomy or cystoprostatectomy and urinary diversion according to each case) in patients with complex genitourinary diseases, three of which were cases of synchronous tumors of the UUT and invasive bladder cancer. All procedures were performed using an open ap-

proach. Wu et al. [13] described a series of 30 patients with end-stage renal disease and TCC. In Asian patients, TCC is the most common urinary carcinoma among patients with uremia, with renal cell carcinoma being the most common among Westerners [14, 15]. There were 3 cases of multiple synchronous urinary tract tumors that underwent total urinary tract extirpation (bilateral nephroureterectomy and simultaneous radical cystectomy, preserving the urethra) in a single procedure. The remaining patients underwent successive extirpations of the urinary tract, increasing morbidity and mortality. Finally, 11 patients underwent complete extirpation of the urinary tract sequentially and 17 underwent bilateral nephroureterectomy (56.7%), concluding that the CUTE procedure in a single act is recommended in patients with dialysis and TCC, bearing in mind that 84% of TCCs were high-grade. Miyake et al. [8] analysed the clinicalpathological characteristics of bladder cancer associated with UUT cancer. Of the 44 cases, 10 patients had a history of bladder cancer, 20 had bladder cancer subsequent to UUT cancer, and 14 had a synchronous tumor in the upper and lower urinary tracts, 9 of which had superficial tumors and 5 invasive tumors in the bladder. Of these 14 cases, only 3 underwent simultaneous nephroureterectomy and cystectomy. A higher incidence of high grade/stage disease in the upper and lower urinary tract, with a significantly lower survival rate, was related to the synchronous tumor group. They concluded that UUT cancer associated with bladder cancer behaves differently depending on the moment in which the tumor appears and that cases of synchronous tumors would benefit from close follow-up and aggressive adjuvant therapy. Barros et al. [16] reported their series of 8 cystectomies with simultaneous laparoscopic nephroureterectomy. Two cases were indicated due to invasive bladder cancer and end-stage renal disease (bilateral nephroureterectomy in both). Of the remaining 6, only 1 showed invasive bladder muscle disease and synchronous tumor of the UUT, with the others being 2 TCC T1G3, 2 TaG3 and 1 multiple Tis, all with synchronous UUT cancer and a history of intravesical chemo- and immunotherapy. To our knowledge, our series is the most extensive published in international literature on simultaneous cystectomy with nephroureterectomy due to invasive bladder cancer with tumors of the UUT.

Regarding the differences of both approaches, we should first point out that the limited number of cases does not allow us to derive sufficient statistical evidence. The overall advantages of the laparoscopic approach include rapid initiation of an oral diet, lower use of narcotic analgesia with better pulmonary rehabilitation and shorter hospitalization and convalescence [17]. There were no differences in hospitalization in our series, but a longer surgery time was observed with less bleeding on average and less need for intraoperative and postoperative transfusion in the laparoscopy group. The results of the laparoscopic approach are comparable to those reported by Barros et al. [16], with a shorter mean surgery time (6.9 hours, range 5.4–10 hours) and less mean bleeding (660 ml, range 450–1,000 ml) but a longer hospitalization (17.8 days, range 8–27 days).

The results obtained for the impact of retroperitoneal lymphadenectomy on survival in our series do not imply any improvement, though they did not involve complete retroperitoneal lymphadenectomy. It was carried out in 6 patients, with a mean of 15 lymph nodes (range 9-23 lymph nodes) being positive in 3 patients (2, 4 and 1 lymph nodes). All of the pN+ died, 1 in the immediate postoperative period and 2 due to metastatic disease. Two of the pN- died, 1 in the postoperative period and the other due to metastatic disease. Of the 6 patients, 5 died. This is a very controversial subject that is currently being studied by different groups. Some indicate a possible improvement in survival rates in invasive urothelial tumors by performing a broad retroperitoneal lymph node dissection, with a 2b level of evidence [18, 19]. Our opinion on retroperitoneal lymph node dissection is to perform it in the presence of enlarged lymph nodes on imaging studies or as intraoperative findings. As such, we cannot compare survival of patients with and without retroperitoneal lymph node dissection as there is a selection bias. In pelvic lymph node dissection, survival appears to improve when more than 14 lymph nodes are removed [20]. The mean number of lymph nodes removed was 13, with 4 patients being positive (3, 12, 3 and 2 lymph nodes). All showed metastatic disease, with 3 dying. Of the remaining 11 pN-, 3 died; 1 in the immediate postoperative period and 2 due to metastatic disease.

In terms of survival, the overall rate in our series was 53.8% (n = 7). Excluding the 2 perioperative deaths, the 2-year survival rate was 38.4%. Among the survivors, all except one (which was a leiomyosarcoma) were high-grade TCC. None had lymph node involvement except for one (pN2, iliac-obturator chain). Four of these were pT3 in the cystectomy and nephroureterectomy, 1 was pT1 in both locations, another pT4 from the UUTc and another was pT2 from the bladder and pT4 from the UUT. Three of these did not receive adjuvant chemotherapy, 3 received cycles of gemcitabine + carboplatin and 1 received 6 cycles of MVAC. These results are

similar to those observed by other groups [8, 15], though the differences in the number of patients and follow-up time mean the series is not comparable. In one single-site study, with a series of 1,054 cases, the overall 5- and 10year survival rates for cystectomy due to invasive cancer were 66 and 43%, respectively [21]. In another study, recurrence-free survival at 5 years depended on staging and lymph node involvement, with 76% for pT1, 74% for pT2, 52% for pT3 and 36% for pT4 [22]. According to the Surveillance, Epidemiology and End Results data, the 5-year survival rate for UUT tumors is 66.5% [23]. The overall 2-year survival rate seen in our series was significantly lower (38.4%). This coincides with the report by Miyake et al. [8], which notes a poorer prognosis for cases with synchronous tumors in the UUT and the bladder than cases with metachronic tumors, showing a higher incidence of high grade and stage tumors in the

former. Nevertheless, studies with longer follow-up and a higher number of cases are needed to validate these statements.

Conclusion

Synchronous UUT tumors and invasive bladder cancer are uncommon. Though multi-center studies with longer follow-up and a greater number of patients are needed, the synchronic presentation seems to influence their prognosis, with lower than expected survival rates for tumors appearing metachronically. Radical cystectomy with simultaneous nephroureterectomy is the treatment of choice as it is a reproducible technique. The laparoscopic approach is reserved for hospitals with experience.

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