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Notizie dalla SIEUN

18° Congresso Nazionale SIEUN

Stresa 17-19 Maggio 2012
Presidente: Dott. Paolo Consonni

CORSO PRECONGRESSUALE
Diagnosi e terapia ecoguidata in urologia nefrologia ed andrologia

Auditorium Casa di Cura Multimedica, Castellanza
Giovedì 17 Maggio 2012 (8.00-13.00)

In diretta dalla sala operatoria
- Posizionamento eco-guidato di nefrostomia percutanea (live o video)
- Biopsia ecoguidata di piccole masse renali
- Biopsie prostatiche ecoguidate (estese, saturazione. "template", transrettali, transperineali)
- Posizionamento eco guidato di "pro-ACT"
- Posizionamento eco guidato di distanziatore per EBRT prostatica
- Posizionamento eco guidato di CVC
- Biopsia eco guidata
- Monitoraggio FAV con ecocolordoppler

CORSO PER INFERMIERI
L'assistenza infermieristica indirizzata all'auto-cura
Hotel Regina Palace - Stresa
Giovedì 17 Maggio 2012 (14.30-18.30)

18° CONGRESSO NAZIONALE SIEUN
Giovedì 17 Maggio 2012
Hotel Regina Palace

14.15 **Main Topic Andrologico**
- Correlazioni cliniche e strumentali delle azoospermie
- Valutazione ecografica con e senza mezzo di contrasto delle sindromi ostruttive delle vie seminali e del testicolo
- Lo scroto acuto
- Faccia a faccia: Ecocolordoppler dinamico penieno nella diagnosi di DE: sì o no?
- Presentazione del libro "Scrotal Pathology"

16.00 **Lettura SIUrO**
16.30 **Sessione Poster**
17.45 **Lettura SIA**
18.15 **Intervento preordinato**
Il "mercato" delle apparecchiature ecografiche in Italia
18.30 **Lettura SIU**
19.30 **Inaugurazione**
21.00 **Cocktail di Benvenuto**

Venerdì 18 Maggio 2012
Hotel Regina Palace

8.00 **Comunicazioni Andrologiche**
9.00 **"Faccia a Faccia"**
La valutazione ecografica preoperatoria dell'IPB: approccio transrettale?
9.45 **Main Topic Urologico**
L'ecografia vescicale oggi:
- Lo studio ecografico delle neoformazioni vescicali: a che punto siamo?
- Valutazione ecografica dello spessore e del peso vescicale, possibili correlazioni con le terapie farmacologiche
- Nefrolitiasi: ESWL, terapia medica e chemioprevenzione delle recidive; ruolo dell'ecografia in uno "Stone Center"
- La valutazione dell'uretere: l'ecografia ha un ruolo?

11.00 **Lettura SIN**
11.30 **Intervento preordinato**
Prostatite e cancro della prostata: ruolo della TRUS e della biopsia prostatica
11.45 **Comunicazioni Urologiche**
13.00 **Lunch**
14.00 **Lettura Auro.it**
14.30 **Main Topic Nefrologico**
La diagnostica ecografica della:
- Nefropatia acuta
- Nefropatia cronica
- Nefropatia ischemica
- Nefropatia da rigetto

15.50 **"Faccia a Faccia"**
Controversie in ecografia nefrologica
L'utilità dei mezzi di contrasto nello studio ecografico del rene
17.00 **Lettura SIUMB**
17.30 **Seduta Amministrativa**

Sabato 19 Maggio 2012
Hotel Regina Palace

8.00 **Comunicazioni Nefrologiche**
9.45 **Main Topic Uroginecologico (SIUD)**
9.45 **"Faccia a Faccia"**
La valutazione preoperatoria della Paziente con incontinenza urinaria: L'ecografia (sovrapubica, transrettale, introitale, transvaginale) *vs* le metodiche radiologiche tradizionali ed innovative (seduta interattiva)
10.25 **Reperti ecografici nell'era della chirurgia protesica**
10.45 **Lettura SUICMI**
11.15 **Premiazione migliori posters e comunicazioni e consegna Premio Giuseppe Pace**
11.45 **Highlights del Congresso**
13.15 **Chiusura del Congresso**

Scrotal Pathology
M. Bertolotto - C. Trombetta

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18° Congresso Nazionale SIEUN – Stresa, 17 - 19 maggio 2012
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ORIGINAL PAPER

Comparison of open and laparoscopic pyeloplasty in ureteropelvic junction obstruction surgery: Report of 49 cases

Paolo Umari, Andrea Lissiani, Carlo Trombetta, Emanuele Belgrano

Department of Urology, University of Trieste, Trieste, Italy

Summary

Objective: *This study aimed to evaluate laparoscopic dismembered pyeloplasty compared with open surgery and to determine whether the morbidity and outcome rates are different in each of these techniques. We report our 10-year experience with open and laparoscopic pyeloplasty at one istitution.*

Methods: *From February 1999 to October 2010, 49 patients with ureteropelvic junction obstruction were assigned into two groups. 25 patients underwent open surgical pyeloplasty (period 1999-2010) and 24 underwent laparoscopic pyeloplasty (period 2004-2010). 25 patients undergoing open pyeloplasty had a retroperitoneal flank approach. Of the 24 laparoscopic cases 18 had a transperitoneal retrocolic access, 1 had a transperitoneal transmesocolic access and 5 had a retroperitoneal access. In all 49 cases an Anderson-Hynes dismembered pyeloplasty was used. We retrospectively compared the operative time, hospital stay, perioperative complications and follow-up of the two groups. Clinical symptoms were assessed before and after surgery, subjectively.*

Results: *Patients dermographic data were similar between the two groups with mean age of 42 years (range 6-78) and with a male/female ratio of 1:1.45. A crossing vessel could be identified in 37.5% (9/24) with laparoscopy vs. 32% (8/25) in open surgery. Compared with open procedures, laparoscopic procedures were associated with a longer mean operating time (274 vs 143 min), a shorter mean hospital stay (9.9 vs 15.8 day) and the perioperative complication rates were 16.7% for laparoscopic pyeloplasties and 20% for open pyeloplasties. The success rates were 90.5% for laparoscopy and 90.9% for open surgery. Average follow-up was 40.9 month for the laparoscopic group and 72.3 month for the open group. Failed procedures showed no improvement in loin pain or obstruction.*

Conclusions: *The efficacy (in term of success rate and perioperative complications) of laparoscopic pyeloplasty is comparable to that of open pyeloplasty, with shorter mean hospital stay and better cosmetic results. These findings may suggest, that the laparoscopic dismembered pyeloplasty has the potential to replace open surgery and may be considered the first option for the treatment of ureteropelvic junction obstruction in expert hands.*

KEY WORDS: *Ureteropelvic junction obstruction; Laparoscopic pyeloplasty; Hydronephrosis; Anderson-Hynes.*

Submitted 13 April 2011; Accepted 30 June 2011

INTRODUCTION

Ureteropelvic junction obstruction leads to progressive dilatation of the renal collecting system and can result in flank pain, urinary tract infections and progressive deterioration of renal function (1, 2). The cause may be functional or anatomical abnormalities or may even be an association between them. Most cases are congenital and are not clinically apparent until later in life (3). It has an excellent surgical treatment outcome (4).

The gold standard treatment for repairing ureteropelvic junction obstruction is open pyeloplasty and best clinical results are reported with dismembering techniques like the Anderson-Hynes procedure (5-7). It is widely used

because it can solve almost all forms of obstruction with success rates exceeding 90% (8, 9).
Laparoscopic pyeloplasty was developed during the early 1990's and recent reports show that it provides success rates of more than 90%, which are absolutely comparable to the open technique (10-18).
Endourologic methods such as endopyelotomy successfully reduced morbidity, but long-term follow-up revealed a 10 to 30% lower success rate in comparison with the open procedure (19, 20). There are some risk factors which decrease further the success rate as the hydronephrosis (lowering the success rate of these procedures from 86% to 50%), the presence of crossing vessels (reducing the success rate from 85% to 54%) and long strictures (21-31).
The idea behind the application of a minimally invasive technique is to achieve the same results with the same safety for the patient and less traumatization when compared to open surgical procedures (32, 33).

Methods

Between February 1999 and October 2010 we performed 49 consecutive pyeloplasties. Patients were assigned into two groups: in the first (open group) 25 patients underwent open surgical pyeloplasty (period 1999-2010) and in the second (laparo group) 24 patients underwent laparoscopic pyeloplasty (period 2004-2010). All surgery was performed with patients under general anesthesia in the lateral flank position with antibiotic prophylaxis.
Twentyfive patients undergoing open pyeloplasty had a retroperitoneal flank approach performed via a subcostal incision above the 12th rib. In all patients a JJ stent was placed intraoperatively except in two cases in which the stent was positioned preoperatively.
Of the 24 laparoscopic cases 18 had a transperitoneal retrocolic access, one had a transperitoneal transmesocolic access and 5 had a retroperitoneal access. Pneumoperitoneum was established usign an open Hasson technique and two or three additional ports were used. A JJ stent was placed in all patients except in one which was a pediatric patient. It was positioned intraoperatively in 13 cases and preoperatively in 10 cases.
In all 49 cases an Anderson-Hynes dismembered pyeloplasty was performed. Initially the ureter was identified in the retroperitoneum. The proximal ureter, ureteropelvic junction and the renal pelvis were completely freed, saving much of the periureteral fat in order to protect as much as possible the ureteral blood supply. The renal pelvis was either dismembered completely and the redundant portion excised. The proximal ureter was then spatulated on its lateral aspect. After that the apex of this lateral, spatulated aspect of the proximal ureter was brought to the inferior border of the renal pelvis. The anastomosis was performed with fine running absorbable sutures, placed full thickness through the ureteral and renal pelvic walls in a watertight manner. In the event that an aberrant vessel was found, this technique enabled the ureteral transposition.
The data collected included patient age, gender, operation time, hospital stay, affected side, presence of aberrant vessels, presence of stones, presence of stent, perioperative complications and follow-up time. We retrospectively compared the operative time, hospital stay, perioperative complications and follow-up between the two groups. Clinical symptoms were assessed before and after surgery, subjectively.

Results

Patients dermographic data were similar between the two groups with mean age of 42 years (range 6-78) and with a male/female ratio of 1:1.45. A crossing vessel could be identified in 37.5% (9/24) with laparoscopy versus 32% (8/25) with open surgery. The presence of stones was 16.7% (4/24) and 32% (8/25) in laparoscopy and open group respectively (Table 1).
By means of a questionnaire we were able to analyze what was the clinical picture of these patients prior to surgery. Symptoms before the treatment were episodes of flank pain in 42 patients (85.7%), urinary tract infections with fever in 16 patients (32.7%) and kidney stone disease in 12 patients (24.5%). Three patients (6.1%) did not show any symptoms related to obstructive disease of the ureteropelvic junction before surgery. In these the diagnosis was made with diagnostic imagining tests performed for other reasons (Table 1). The preoperative diagnosis

Table 1.

Patient characteristics.

	Open group	Laparo group
Number of patients	25 (51%)	24 (49%)
Mean age	46.5 (range 20 - 78)	37.5 (range 6 - 59)
Gender		
Male	9 (18.4%)	11 (22.4%)
Female	16 (32.7%)	13 (26.5%)
Side		
Right	12 (24.5%)	12 (24.5%)
Left	13 (26.5%)	12 (24.5%)
Presence of crossing vessel	8 (32%)	9 (37.5%)
Presence of stones	8 (32%)	4 (16.7%)
Stent		
Stentless	0 (0%)	1 (4.2%)
Preoperatively	2 (8%)	13 (54.2%)
Intraoperatively	23 (92%)	10 (41.7%)
Indication for surgery		
Asymptomatic	3 (6.1%)	
Loin Pain	42 (85.7%)	
Urinary Tract Infection	16 (32.7%)	
Kidney Stone Disease	12 (24.5%)	

included a detailed clinical history with particular attention to the nature of pain, sonography, excretory urography, renal scintigraphy and retrograde pyelography.
Follow-up of patients was done by careful analysis of diagnostic imagining examinations performed after discharge and the use of a questionnaire. The average duration of follow-up was 40.9 months (range 7-75 months) in the laparo group and 72.3 months (range 9-154 months) in the open group.
In the laparo group it was possible to follow-up 21 patients out of 24, because 3 patients were enrolled too late to have a significant follow-up period. Of the 21 patients screened, all performed at least one follow-up imaging study; 71.4% had at least one sonogram, 33.3% at least one IV urogram, 23.8% at least one CT scan and 9.5% at least one nuclear scan. The follow-up showed that 19 patients had resolution of symptoms and improvement of hydronephrosis documented by diagnostic imaging studies and that 2 patients had not improve clinical status after surgery: the first had recurrent episodes of colic pain and the second presented a kidney stone disease on the side of the intervention (Table 1).
In the open group it was possible to follow-up 22 patients out of 25, since the remaining 3 could not be contacted. Of the 22 patients screened, all performed at least one follow-up imaging study; 72.7% had at least one sonogram, 31.8% at least one IV urogram, 9.1% at least one CT scan and 18.2% at least one nuclear scan. The follow-up showed that 20 patients had resolution of symptoms and improvement of hydronephrosis documented by diagnostic imaging studies; 2 patients had no improved clinical status after surgery: the first required three additional interventions including a radical nephrectomy and the second had recurrent episodes of colic pain from persistent kidney stones (Table 1).
The mean operative time (consisting of cystoscopy, JJ stent placing and surgical repair) was 274 minutes (range 175-410) and 143 minutes (range 85-215) in laparo and open group respectively (Table 2).
The mean postoperative stay was 9.9 days (range 6-22) and 15.8 days (range 6-52) in laparo and open group respectively (Table 2).
In the laparo group there where complications in 4 patients. In one patient, isolation of the pelvis was extremely difficult making it necessary to convert to an open operation. In another patient passing the stent was difficult, so we were able to properly position the stent by ureterocystoscopy. One patient experienced an episode of respiratory distress that was rapidly treated with oxygen therapy and, finally, one patient had a minor surgical wound complication, which resolved in a few days (Table 2).
In the open group there where complications in 5 patients, including a small breach of the parietal peritoneum, which was promptly sutured; an episode of chest pain with signs of ischemia detected by electrocardiography but without subsequent rise in cardiac enzymes; an episode of acute retention of urine following removal of bladder catheter and finally, two patients experienced minor complications of the surgical wound, which resolved in a few days (Table 2).
The estimated success rates were 90.5% for laparoscopy and 90.9% for open surgery, with an average follow-up of 40.9 month and 72.3 month respectively. Failed procedures showed no improvement in loin pain or obstruction.

Table 2.

Results.

	Open group	Laparo group
Mean operative time (min)	143 (85-215)	274 (175-410)
Mean hospital stay (days)	15.8 (6-52)	9.9 (6-22)
Perioperative complications (tot)	(20%)	(16.7%)
Peritoneal breach	1	0
Chess pain	1	0
Acute retention of urine	1	0
Wound dehiscence	1	0
Wound pain	1	0
Postoperative pain	0	1
Conversion to open	0	1
Stent-related	0	1
Respiratory distress	0	1
Patients with follow-up	22	21
Average follow-up (months)	72.3 (9-154)	40.9 (7-75)
Follow-up examination performed		
Sonography	72.7%	71.4%
Urography	31.8%	33.3%
CT scan	9.1%	23.8%
Scintigraphy	18.2%	9.5%
None	0%	0%
Follow-up results		
Resolution	20	19
No resolution	2	2
Could not be contacted	3	0
Not significant follow-up	0	3
Success rate	90.9%	90.5%

Discussion

Ureteropelvic junction obstruction is an entity that should be promptly diagnosed and treated to prevent the progressive loss of function in the affected renal unit. In adults it should be suspected in any patient with relapsing colicky pain, especially after ingestion of large amount of water, and frequent episodes of urinary tract infection with fever (1).
There is a correlation between residual renal function and probability of recovery after resolution of the stenosis, so it is always worth considering the possibility of surgery assessing the risks and benefits from case to case (34, 35).

Table 3.

Comparison with other studies.

	Number of patients		Mean operative time (min)		Mean hospital stay (days)		Perioperative complications (%)		Success rate (%)	
	OPEN	LAPARO	OPEN	LAPARO	OPEN	LAPARO	OPEN	LAPARO	OPEN	LAPARO
Brooks J. (10)	11	12	28	356	7.3	3.1	18	25	100	100
Bauer J. (11)	35	42	/-/	/-/	/-/	/-/	11	12	94	98
Soulié M. (12)	28	26	145	165	5.5	4.5	14.3	11.5	89.2	92
Klingler H. (13)	40	15	/-/	/-/	13.4	5.9	40	17.5	93.4	96
Simforoosh N. (14)	32	37	132	192	6.2	6.2	6.2	24	96.5	89
Zhang X. (15)	40	56	80	120	9	7	7.5	3.6	98.2	97.5
Troxel S. (16)	13	19	200	231	3.3	2.4	7.7	5.3	100	94.7
Bansal P. (17)	34	28	122	244	8.3	3.1	0	7.1	100	96.4
Calvert R. (18)	51	49	91	159	5.6	5.4	24	17	96	98
Our series	**25**	**24**	**143**	**274**	**15.8**	**9.9**	**20**	**16.7**	**90.9**	**90.5**

The definitive treatment of ureteropelvic junction obstruction is surgical and there are many techniques available nowadays. The ideal treatment would have the highest success rate, be capable of correcting all forms of UPJ obstruction, be capable of removing coexisting renal calculi and be minimally invasive (9). In the last 20 years the treatment of ureteropelvic junction stenosis has been significantly influenced by various minimally invasive techniques, including percutaneous and ureteroscopic endopyelotomy, cutting transvesical baloon dilatation as well as laparoscopic pyeloplasty (2,36). All of these procedures were introduced with the goal to meet the standard of open dismembered pyeloplasty providing long-term success of more than 90%, with a lower surgical trauma for the patient (33, 37). In recent years the laparoscopic pyeloplasty is providing an increasingly viable alternative to open pyeloplasty, in fact it reproduces all steps of open pyeloplasty such as dissection, excision of the ureteropelvic junction, ureteral spatulation and anastomosis (3).

The laparoscopic pyeloplasty is applicable to both primary and secondary ureteropelvic juncton obstruction, to all age groups even in the presence of anatomical variations of the ureteropelvic region, aberrant vessels and high insertion of the ureter that have proven to be able to compromise outcomes of endourological procedures (7).

Several scientific studies have analyzed and compared different points of view regarding the performance of pyeloplasty with open and laparoscopic technique (10-18). Results in the short and medium term obtained confirms that the laparoscopic pyeloplasty has the same success rate of open pyeloplasty in both children and adults, but with the benefits of being a minimally invasive technique. The main benefits are: less invasiveness in terms of wound size, less postoperative pain, fewer days of hospital stay and better cosmetic results (14, 38, 39). This may be of particular importance in young (female) patients where an excellent cosmetic result should be offered for treatment of benign disease (9). The possibilities of less patient morbidity reduces length of stay and accordingly lowers hospital costs (40). The minimal trauma to the abdominal wall also avoids the formation of abdominal wall herniation (9).

We compared our experience with other published international studies and our results do not differ significatly from these (Table 3). In fact most papers reported case series with results that are comparable with our experience with operative time ranges between 89 and 300 minutes, complication rates between 10% and 25% and success rates between 75% and 100%. Sometimes some authors report a shorter or a longer operative time in the group treated with laparoscopic pyeloplasty and this is due to the fact that some studies do not include the time spent on positioning the stent, which on everage takes from 15 to 45 minutes.

Laparoscopic pyeloplasty is a technically difficult procedure that has a long learning curve and requires very good training, especially for suturing. Several studies quantify this learning curve in 30-50 cases, referring of course to surgeons who have never performed any type of laparoscopic surgery (3, 18, 41, 42).

In view of the steep learning curve involved in laparoscopic pyeloplasty, many surgeons have choosen to opt for a robotically assisted technique (43). The main advantage of robotic assistance is to allow a minimally invasive procedure to be performed by a surgeon without prior formal laparoscopic training. That procedure, with the daVinci robotic system, results in faster suturing and overall more rapid surgery. Although the results are promising, more experience and clinical follow-up with this new technique is needed to confirm the efficacy of this new surgical approach (44).

Conclusion

In our experience, results obtained demonstrate that: the success rate is similar in both groups and compared with open procedures, laparoscopic procedures were associated with longer mean operating time (274 vs 143 min), shorter mean hospital stay (9.9 vs 15.8 day), same periopera-

tive complication rate (16.7% vs 20%) but with the benefits of being a minimally invasive technique. This findings may suggest, that the laparoscopic dismembered pyeloplasty has the potential to replace open surgery and may be considered the first option for the treatment of ureteropelvic junction obstruction in expert hands. At our institution the laparoscopic Anderson-Hynes dismembered pyeloplasty has become the first option in the treatment of ureteropelvic junction obstruction.

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ORIGINAL PAPER

Transperitoneal versus retroperitoneal laparoscopic partial nephrectomy: Initial experience

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Summary

Objective: *We present the transperitoneal and retroperitoneal approaches to laparoscopic partial nephrectomy and compare the outcomes of each technique.*

Methods: *Between December 2006 and March 2010, retroperitoneal laparoscopic partial nephrectomy (RLPN) was performed in 23 patients and transperitoneal laparoscopic partial nephrectomy (TLPN) in 26 patients. They were compared regarding surgical technique, operative parameters, postoperative recovery and follow-up data. The 2 approaches used similar operative techniques to control parenchymal bleeding.*

Results: *The patient demographics were similar in both groups. The mean tumour size was 3.1 cm in the retroperitoneal group and 3.4 cm in the transperitoneal group. The difference was not statistically significant (p: 0.095). The mean operative time was significantly longer in the transperitoneal group (215 vs 185 minutes, p: 0.031). The mean warm ischemia time difference was not statistically significant (25 vs 28 minutes, p: 0.102). The mean estimated blood loss (EBL) was greater in the transperitoneal group (254 vs 204 cc, p: 0.003). Moreover, the mean hospital stay was 4.1 days in the RLPN and 4.3 days in the TLPN group (p: 0.303) The difference was not statistically significant. The median follow-up was 11 months (range: 2 to 35) in the retroperitoneal group and 13 months (range 1 to 36) in the transperitoneal group.*

Conclusions: *Our experience has shown that laparoscopic partial nephrectomy is a safe, feasible technique for patients with small exophytic renal tumours. We believe that the decision regarding the approach should be based on the tumor location on the kidney surface.*

KEY WORDS: *Laparascopy; Partial nephrectomy; Renal tumour.*

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INTRODUCTION

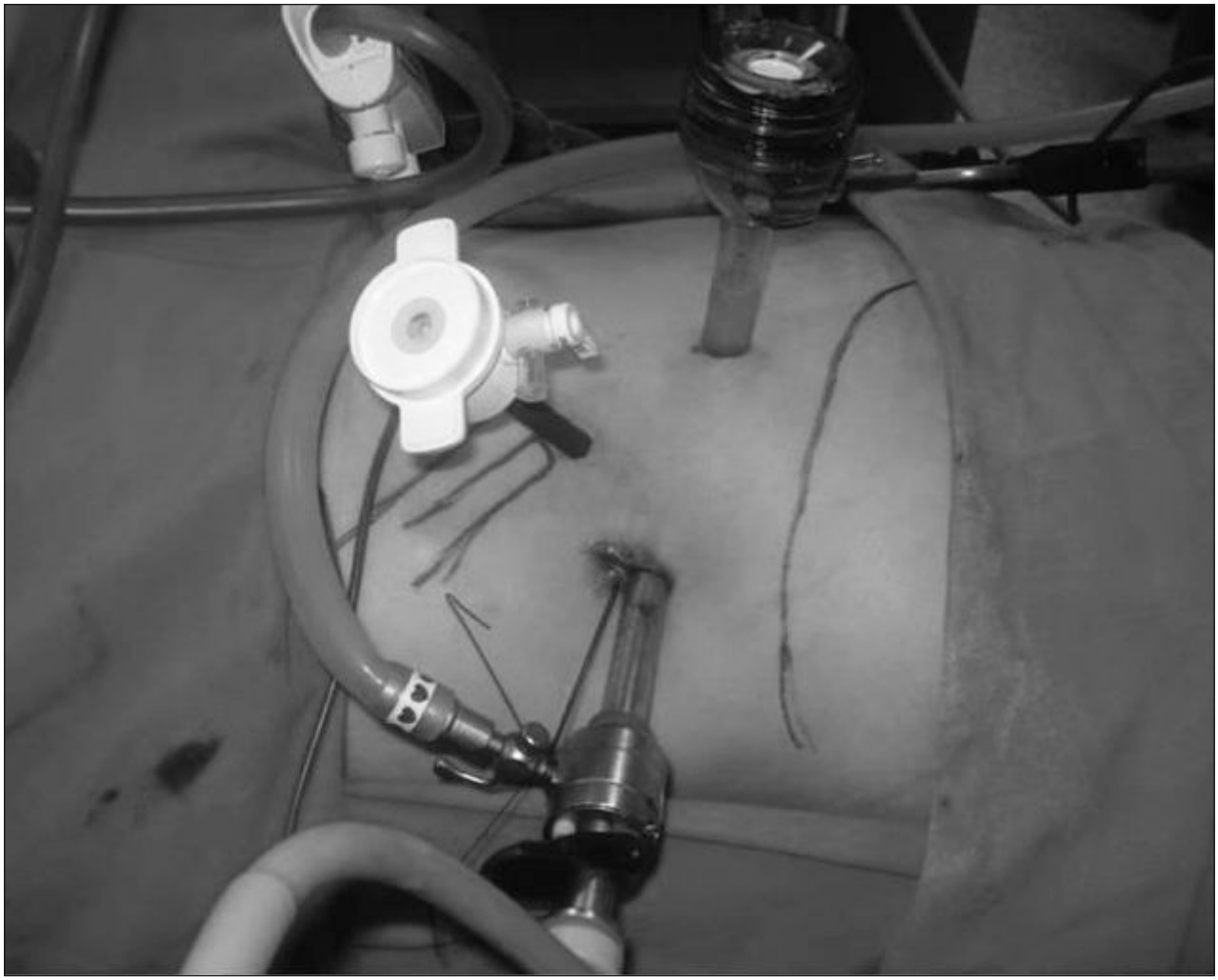
The widespread use of computed tomography, ultrasonography and magnetic resonance imaging has increased the detection of incidental small localized renal tumours (1). Traditionally, radical nephrectomy was used as standard surgical treatment, but open or laparoscopic partial nephrectomy has gained popularity with long-term oncological outcomes and renal parenchymal preservation. Moreover, partial nephrectomy has been used safely for polar tumours up to 7 cm in diameter (2). Even if laparoscopic partial nephrectomy (LPN) is much more complicated because of the need for the completion of tumor excision, pelvicalyceal system repairing and renal parenchymal suturing within reasonable warm ischemia time, it gained popularity in the last decade. On the other hand with experienced surgeons and appropriate patient selection, LPN is feasible and efficacious for kidney tumours > 4 cm (3). We performed laparoscopic partial nephrectomy using two surgical approach because not all renal masses are accessible with the same technique. We report our experience with the transperitoneal and retroperitoneal laparoscopic partial nephrectomy and compare the outcomes of each technique.

MATERIAL AND METHODS

Between December 2006 and March 2010, 49 patients underwent laparoscopic partial nephrectomy (LPN) by a single surgeon (VT) for organ confined tumors on preoperative imaging. Three-dimensional Computed Tomography (CT) was utilized to evaluate the size, location and depth of the renal mass and also to assess renal anatomy and vasculature in all patients. Metastatic evaluation was completed using chest x-ray and liver function studies.

Figure 1.

Port placement for laparoscopic retroperitoneal partial nephrectomy.



Indications for nephron sparing surgery were small, exophytic solitary renal tumor and they were similar in the two groups. The choice of the laparoscopic approach was at the discretion of the surgeon and it was dictated primarily by the location of the renal mass. The transperitoneal approach was generally used for anterior, medial lesions. The retroperitoneal approach was generally used for posterior, lateral lesions. We did not routinely perform preoperative ureteric catheterization. Patients with a renal mass near collecting system and large renal mass underwent cystoscopy and ureteral catheterization with a 5 F open end ureteral catheter prior to positioning for the laparoscopic procedure. The ureteral catheter was then secured to a Foley catheter and prepared for later retrograde injection of Methylene Blue.

In retroperitoneal approach after retroperitoneal access and balloon dilation on the patient in lumbotomy position, the procedure was performed through trocars located on the middle, anterior and posterior axillary lines (Figure 1). In transperitoneal approach, the patients were placed in the modified flank position.

Pneumoperitoneum was achieved by transperitoneal Hasson technique. Three ports were used. For right tumors an additional trocar is placed in the midline epigastrium to retract the liver. After pneumoperitoneum was obtained, the colon was reflected medially and kidney exposed using standard laparoscopic techniques. In retroperitoneal and transperitoneal approach once the renal pedicle was identified, the main artery was isolated and secured with an elastic loop clipped on its distal end. Vascular control of renal vein were only applied for large renal lesions and renal vein was not clamped in any operation.

After the tumour was identified, it was resected by aid of cold scissors. Renal artery was not occluded by locking a vascular control strip in one retroperitoneal case. The tumour was resected by aid of harmonic scalpel (tumour size < 2 cm). We did not need frozen section for any patients. After tumour excision any collecting system entry was repaired with a running 3/0 vicryl suture on a CT-1 needle. After placement of a surgicel into tumor bed, the parenchymal repair was accomplished by 2/0 vicryl suture. To minimise knot tying, Hem-o-lok clips

were used to secure the ends of the suture. In recently performed partial nephrectomies to complete collecting system entry repair with shorter warm ischemia time, suture is passed 2 cm from the cut edge of the resection bed into the base of the defect. The end of the suture is preloaded with a 5-mm locking Hem-O-Lok clip and knotted. The suture is then run along the base of the defect closing the collecting system, adjacent muscular arterial branches, and central venotomies without positioning surgicel. The leading edge of the suture is maintained on tension during the entire run, and the final throw is brought out the renal capsule opposite the site of entry. The suture is then cinched down and secured with a locking hemoclip, further compressing the defect. The specimen was placed in a laparoscopic bag before removed via the camera port. A perirenal drain was placed prior to closing the wound.

Study groups were retrospectively compared using student t test and Mann Whitney U test. Patient demographics, preoperative data, and operative and postoperative outcomes were performed to compare patient groups. $P < 0.05$ was considered statistically significant.

Results

Table 1 compares preoperative parameters in the 23 patients undergoing retroperitoneal laparoscopic partial nephrectomy (RLPN) and the 26 undergoing transperitoneal laparoscopic partial nephrectomy (TLPN). The mean age was 60 years in the retroperitoneal group and 59 years in the transperitoneal group (p: 0.516). BMI was 27.4 ± 3.6 kg/m^2 in the retroperitoneal group and 28.1 ± 2.9 kg/m2 in the transperitoneal group (p = 0.502). There were 24 right and 25 left renal masses. Tumor location on the kidney surface was variable (Table 1). The mean tumour size was 3.1 cm (range: 1.8-4.1) in the retroperitoneal group and 3.4 cm (range: 2.1-4.2) in the transperitoneal group. The difference was not statistically significant (p: 0.095).

Table 2 compares operative and postoperative parameters in the 23 patients undergoing RLPN and the 26 undergoing TLPN. The mean operative time was significantly longer in the transperitoneal group (215 *vs* 185 minutes, respectively, p = 0.031). The mean warm ischemia time was 25 minutes in the transperitoneal group and 28 minutes in the retroperitoneal group. The difference was not statistically significant (p = 0.102). The mean estimated blood loss (EBL) was also more in the transperitoneal group (254 *vs* 204 cc, p = 0.003). No difference in preoperative and postoperative creatinine levels existed between two groups. Seven patients were identified intraoperatively to have entrance into the collecting system, four of them in the transperitoneal and the remaining three in the retroperitoneal group. The collecting system repair was accomplished by 3/0 vicryl suture. Two patients in the retroperitoneal and one patient in the transperitoneal group had postoperative persistent urine leakage. Three patients required postoperative ureteral stent for persistent urinary leakage. The leaks were subsequently resolved and the stents were removed. In the TLPN group minor complications included postoperative ileus in two patients. There was no open conversion.

None of the patients required blood transfusion perioperatively and postoperatively. No other perioperative and postoperative complications were encountered. The mean time of the removal of the drain was 2.4 days (range: 1-8) postoperatively in the RLPN group and 2.9 days (range: 1-7) postoperatively in the TLPN group (p = 0.098). Moreover the mean hospital stay was 4.1 days (range: 3-9) in the RLPN and 4.3 days (range: 3-8) in the TLPN group. The difference was not statistically

Table 1.

Preoperative parameters.

	RLPN	TLPN	p
n	23	26	
Age (years) (mean ± SD)	60.40 ± 5.49	59.25 ± 4.87	**0.516**
BMI (kg/m^2) (mean ± SD)	27.4 ± 3.6	28.1 ± 2.9	**0.502**
Tumour size (mm) (range)	3.13 ± 0.51	3.43 ± 0.56	**0.096**
Preoperative creatinine (mg/dl) (range)	1.01 (0.6-1.3)	0.96 (0.6-1.4)	**0.509**
Tumour side (%)			
Right	13 (56.5%)	11 (42.3%)	
Left	10 (43.5%)	15 (57.7%)	
Tumour location (%)			
Posterior	14 (60.8%)	0	
Lateral	9 (39.2%)	0	
Anterior	0	17 (65.3%)	
Medial	0	9 (34.7%)	
Tumour pole site (%)			
Upper	13 (56.5%)	8 (30.7%)	
Mid	6 (26.1%)	8 (30.7%)	
Lower	4 (17.4%)	10 (38.6%)	

Student t test, n: number, RLPN: retroperitoneal laparoscopic nephrectomy, TLPN: transperitoneal laparoscopic partial nephrectomy. *p < 0.05

Table 2.

Operative and postoperative parameters.

	RLPN	TLPN	p
n	23	26	
Operative time (minutes) (range)	185 (165-280)	215 (145-340)	**0.031***
Warm ischemia time (minutes) (range)	28.4 (15-36)	25.2 (12-37)	**0.102**
Estimated blood loss (ml) (range)	204.1 (165-280)	254.3 (125-390)	**0.003****
Pelvicalyceal system repair (%)	3 (13%)	4 (15%)	**0.509**
Postoperative creatinine (mg/dl) (range)	1.20 (0.9-1.6)	1.12 (0.8-1.5)	**0.137**
Complications (%)			
Ileus	0	2 (7.6%)	
Persistent urinary leakage	2 (8.6%)	1 (3.8%)	
Drain removal (days) (mean ± SD)	2.40 ± 1.73	2.94 ± 1.61	**0.098**
Hospital stay (days) (mean ± SD)	4.15 ± 1.42	4.37 ± 1.31	**0.303**
Mean follow-up (months) (range)	11.45 (2-35)	13.5 (1-36)	**0.566**

Student t test, *Mann-Whitney U test, n: number, RLPN: retroperitoneal laparoscopic nephrectomy, TLPN: transperitoneal laparoscopic partial nephrectomy. *p < 0.05, **p < 0.01

significant (p = 0.303). Pathological examination revealed 22 renal cell carcinoma (16 clear cell, 5 papillary, 1 chromophobe) and 1 angiomyolipoma in the RLPN patients, 25 renal cell carcinoma (18 clear cell, 6 papillary, 1 chromophobe) and 1 oncocytoma in the TLPN patients. The pathological results are given in table 3. The surgical margins were negative in all cases. The mean follow-up was 11 months (range: 2 to 35) in the retroperitoneal group and 13 months (range: 1 to 36) in the transperitoneal group. We did not observe any local recurrence or far metastasis in no patiens.

Table 3.

Pathological outcomes.

	RLPN	TLPN
n	23	26
Renal cell carinoma	22 (96%)	25 (96%)
Clear cell	16 (73%)	18 (72%)
Papillary	5 (22%)	6 (24%)
Chromophobe	1 (5%)	1 (4%)
Oncocytoma	0	1 (4%)
Angiomyolipoma	1 (4%)	0
Stage (pT)		
pT1a	19	21
pT1b	3	4
Fuhrmann grade		
1	14	14
2	6	9
3	2	2
4	0	0

n: number, RLPN: retroperitoneal laparoscopic nephrectomy, TLPN: transperitoneal laparoscopic partial nephrectomy.

Discussion

With better access to medical care and the latest imaging modalities, up to 50% of patients are being diagnosed with incidental renal tumours. Of these, about 15% may prove to be benign upon histological examination (4). Subjecting these patients to radical nephrectomy may be over treatment, especially when the tumours prove to be benign later. Although the accuracy of percutaneous biopsy has improved (5, 6), indeterminate biopsies still exist and are subject to interobserver variability (5, 7, 8). Laparoscopic nephron sparing surgery was first performed clinically in 1993 by *Winfield et al.* for benign disease (9). Since then, other groups have reported successful outcomes with laparoscopic partial nephrectomy for benign and malignant disease and reported results that compare favorably with those of open partial nephrectomy (9, 11, 12).

The transperitoneal (10) and the retroperitoneal (13) approaches have been used for laparoscopic partial nephrectomy. Retroperitoneal technique has some obvious advantages as prompt and direct access to the renal hilum and great vessels, in morbidly obese patients and in those who have undergone prior transperitoneal surgery.On the other hand, this approach has some disadvantages as a small working space, limited landmarks and the risk of becoming disoriented and causing inadvertent injury (14). Another advantage of the retroperitoneal approach is the containment of surgical intervention products (blood and urine) outside the peritoneum, which we think minimizes postoperative ileus. In our study, in the TLPN group, postoperative ileus was observed in two patients.

The transperitoneal approach is disadvantages with requirement of bowel mobilization to expose the kidney, on the other hand offers a greater working space and familiar landmarks. Additionally, transperitoneal access may be challenging for posterior renal masses and full kidney mobilization may be required to visualize the mass.

Our primary decision making parameter to select the laparoscopic approach to LPN was tumor location. The transperitoneal approach was generally used for anterior lesions while the retroperitoneal approach was generally used for posterior lesions.

One of the most crucial steps during LPN is the control of the hilum. Several techniques to secure the hilum have been described (15, 16). The renal artery can be safely secured with locking clips or with an endovascular stapler. In our study for retroperitoneal and transperitoneal approaches after the renal pedicle was identified, the main artery was isolated and secured with an elastic loop clipped on its distal end. Vascular control of renal vein were only applied for large renal lesions and renal vein was not clamped in any operation. *Pyo et al.* only clamped renal veins when lesions involved central venous sinuses or were adjacent to main hilar vessels (17).

Gill et al. compared the two surgical technique in their 163 case series. They found longer operation time (3.5 and 2.9 hours respectively) and warm ischemia time (31 and 28 minutes respectively) in TLPN group compared to the RLPN group because the tumour size in TLPN group was larger than the RLPN group. But there were no statistical significance in terms of bleeding, perioperative complications and postoperative creatinine levels (18). In our series, mean operation time was significantly longer in the transperitoneal group (215 *vs* 185 minutes, p: 0.031) and warm ischemia time was not statistically different between the two approaches (25 *vs* 28 minutes, p: 0.102). Even, the difference is not statistically significant, warm ischemia time was longer in retroperitoneal approach due to difficulty in putting sutures in smaller working space compared with transperitoneal approach. The mean estimated blood loss (EBL) was also more in the transperitoneal group (254 *vs* 204 cc, p = 0.003). No difference in preoperative and postoperative creatinine levels existed between two groups. The mean time of the removal of the drain was 2.4 days postoperatively in the RLPN group and 2.9 days postoperatively in the TLPN group (p = 0.098). Mean hospital stay was 4.1 days in the RLPN and 4.3 days in the TLPN group (p = 0.303).

The goal of laparoscopic partial nephrectomy should be safe removal of the renal segment in question, while maintaining acceptable hemostasis, adequate operative visualization and closure of any entry into the collecting system. There are a variety of hemostatic agents such as *FloSeal* (19), *Tachosyl* (19), *fibrin glue* (19), *Argon beam laser* (19), *Surgicel Bolster* (19), *LapraTy clips* (19), *hemolock clips* (19), *renal snares* (20), *bipolar cautery* (21), *harmonic scalpel* (21), *holmium laser* (22). In our series after placement of a surgicel into tumor bed, the parencymal repair was accomplished by 2/0 vicryl suture. To minimise knot tying, Hem-o-lok clips were used to secure the ends of the suture. We believe that the combination of renal hilar clamping with excision of the mass with cold scissors allows excellent visualization of the normal renal parenchyma during dissection. For large blood vessels oversewing with intracorporeal sutures is required. The most common complication following open partial nephrectomy is urine leakage with a mean reported incidence of 6.5% (range 1.4% to 17%) (23).

In the laparoscopic literature, the urine leakage rate in early series was 5.9% to 28.5%. (8, 21, 24, 25). However, in recent series that have used collecting system oversewing the urine leakage rate is 0% to 2% (7,26). In our series the seven patients were identified intraoperatively to have entrance into the collecting system, including four (15%) in the transperitoneal and three (13%) in the retroperitoneal group. The collecting system repair was accomplished by 3/0 vicryl suture. Two patients in the retroperitoneal and one patient in the transperitoneal group had postoperative persistent urine leakage. Three patients required postoperative ureteral stent for persistent urinary leakage. The leaks were subsequently resolved and the stents were removed. We believe that retrograde injection to assess collecting system entry is an important step in laparoscopic partial nephrectomy, especially for tumors that are close to the collecting system.

The positive margin rate after LPN has been reported to be in the range of 1.8 to 2.4 % (27, 28). In our study the surgical margin was negative in all cases.

In patient groups on which nephron sparing surgery was performed, a local recurrence rate between 0% and 7.3% (23,29) has been reported. *Becker et al.* found recurrent tumour in 12 (5.5%) of 216 patients in their nephron sparing surgery patients with unilateral, small tumour after 66 months follow-up period (30). We found no local or far recurrence in our 11 months (range: 1-36) follow-up case series.

Conclusions

LPN is accepted as a less invasive method in comparison with other therapeutic alternatives in the treatment of renal tumors. Our experience has shown that laparoscopic partial nephrectomy is a safe, feasible technique for patients with small exophytic renal tumours. We believe that the decision on the approach should be based on the tumour location on the kidney surface. The transperitoneal approach was generally used for anterior medial lesions. The retroperitoneal approach was generally used for posterior lateral lesions. The type of procedure used (retroperitoneal or transperitoneal) is directly related to the percentage of success in safe removal of the tumour.

Disclosure statement

No competing financial interests exist.

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ORIGINAL PAPER

Comparison of p38MAPK (mitogene activated protein kinase), p65 NFkB (nuclear factor kappa b) and EMMPRIN (extracellular matrix metalloproteinase inducer) expressions with tumor grade and stage of superficial and invasive bladder tumors

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Summary

To identify the molecular mechanisms of bladder cancer invasion pathophysiology. To assess EMMPRIN, p65NFkB and p38MAPK expressions which play a role in signal transmission system of muscle and non muscle invasive bladder tumors. Fifty-seven patients with non muscle invasive tumors (mean age 65.2 ± 16.1) and 34 patients with muscle invasive tumors (mean age 62.2 ± 20.7) were included in this study. Normal tissue from the same patients' bladders were used as control group. Patients had either TUR or radical cystectomy and paraffin sections were prepared for immunohistochemistry. Expression density was evaluated semiquantitively according to tumor grade and invasion depth. Results were compared with Mann Whitney U, Wilcoxon W, Chi Square and variation analysis tests. MAPK and EMMPRIN expression was increased according to tumor grade ($p < 0.05$). These expressions were also significantly higher in muscle invasive tumors than in non muscle invasive ones ($p < 0.05$). In normal tissue samples of both TUR and radical cystectomy materials, EMMPRIN, NFkB and MAPK expressions were lower than in tumor samples ($p < 0.05$). NFkB wasn't related to tumor grade/stage ($p > 0.05$). It can be stated that MAPK and EMMPRIN expression is related to the grade of bladder tumor and that NFkB positivity is not related to the grade/stage of the disease. In future positivity of lymph nodes and visceral metastasis and survival must be assessed to define the relationship with the expressions in long term follow up studies involving a larger number of patients.

KEY WORDS: Bladder cancer, NFkB, MAPK, EMMPRIN, Immunohistochemistry.

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INTRODUCTION

Tumor local invasion and distant metastasis require the breakdown of extracellular matrix (ECM) via specific intracellular signalling pathways. For this purpose some studies identified extracellular matrix metalloproteinase inducer (EMMPRIN) a.k.a. CD147 - a transmembrane glycoprotein which degrades ECM by stimulating fibroblast matrix metalloproteinase (MMP) enzymes in certain cancer cells (1).
Nuclear factor kappa b (NFkB) notably p65 protein functions during DNA (deoxyribonucleic acid) transcription and takes action against cytokines, oxidative stress, free radicals, ultraviolet (UV) radiation, low density lipoprotein (LDL) oxidation and bacterial/viral antigens in the cell (2-6). Nuclear p65 initiates the transcription of a wide variety of genes that code for angiogenic factors, cell adhesion molecules, antiapoptotic factors and cytokines, which are involved in cell survival, tumour invasion and metastasis. Extensive studies performed on cancer cell lines and preclinical models support a role of NFkB in cancer devel-

opment and progression (7). Mitogen-activated protein kinase (MAPK) pathways are key regulatory pathways for the control of growth and the induction of stress responses in cells (8). Thus inhibitors of stress activated p38MAPK reduce in vitro invasion of malignant melanoma cells (9).
In this study we tried to describe and compare the relationship of EMMPRIN, p38MAPK and p65NFkB expressions in superficial and invasive bladder tumors.

Materials and Methods

Fifty seven (47 males, 10 females) patients with primary superficial urothelial bladder tumors who had undergone transurethral resection of bladder tumor (TUR-BT) in the urology clinics of Okmeydani and Vakif Gureba Training and Research Hospitals between January 2006 and June 2010 were included in this study. Patients with previous recurrent tumors, intravesical immunotherapy/chemotherapy were excluded from the study.
Thirty four (31 males, 3 females) patients with invasive urothelial bladder tumors who had undergone radical cystectomy in the same time period in the aforementioned clinics were included in the study. Patients with previous radio- or systemic chemotherapy were excluded from the study.
For both of the superficial and invasive tumors, paraffin embedded tissue samples with the most invasive tumors were selected by the pathologist and irrelevant samples such as lymph nodes, ureters, prostate, uterus/adnexial structures, etc. in cystectomy patients were not taken into the study.
Antibodies used in the study are as follows; EMMPRIN (8D6): sc-21746 (SantaCruz Biotechnology Inc., CA, USA): Mouse monoclonal antibody. NFkB p65 (F-6): sc-8008 (SantaCruz Biotechnology Inc., CA, USA): Mouse monoclonal antibody. p38α/β (H-147): sc-7149 (SantaCruz Biotechnology Inc., CA, USA): Rabbit polyclonal antibody.
To identify the p65NFkB and p38MAPK expressions we performed immunohistochemical staining in all groups; 3-4 µ sections from 10% formaline fixated and paraffin embedded blocks were prepared. These sections were put on Poly-L-Lysine coated stages. Sections were taken to incubator at 58°C for 80 minutes, put into the xylene three times for 5 minutes. 100% ethanol was applied twice for 3 minutes, then 95% and 80% ethanol were applied twice for 3 minutes each. Deparaffinization procedure ended with distilled water washing. Sections were dipped into the citrate buffer solution and heated in the microwave oven 4 times for 5 minutes. Sections were cooled down at room temperature for 20 minutes; 10 minutes of incubation with trypsine was made according to p38 data sheet. After that stages were taken to the PBS (phosphate buffered solution). After that the stages dried, lines were drawned around the sections with hydrophobic pen. Then the stages were put into PBS. To decrease the nonspecific stage staining, hydrogen peroxide was applied for 10 minutes. Stages were washed with PBS three times. Under room temperature Ultra V Block procedure was performed for 10 minutes. Only spilling the excess Ultra V Block from the stages without washing, p65 NFkB and p38 MAPK, both diluted to 1/100, were dripped to cover the entire tissue sections and then incubated for 45 minutes. Sections were washed with PBS three times. Primary antibody enhancer was applied and the sections were incubated for 20 minutes at room temperature. Again sections were washed with PBS three times. After a HRP (horse radish peroxidise) polymer incubation period of 30 minutes, sections were washed with PBS three times. AEC (3-amino-9-ethylcarbazole) chromogen was dripped and then incubated for 15 minutes. Chromogen had been prepared 1 minute before the procedure. Stages were washed with distilled water. Counterstaining with Mayer's Hematoxylin was performed for 1 minute. Then stages were washed with tap water. Finally all of the stages were closed with aqueous closing materials.
For the EMMPRIN immunohistochemical staining, the following procedures were performed. After deparrafinization, 15 minutes of incubation in the microwave oven with 10mM citrate buffer were done. To block the endogenous peroxidise activity, 3% hydrogen peroxidase was used. Nonspecific blockage with background-sniper and then 10 minutes of room temperature incubation followed. Overnight incubation at 4°C with primary antibody was achieved. Next morning 15 minutes of incubation with secondary antibody was done: 15 minutes of incubation with HRP and 5 minutes of incubation with DAB (3,3'-diaminobenzidine) were performed. Counterstaining with Mayer's Hematoxylin was performed for 1 minute. After dehydration, all the stages were closed with aqueous closing materials.
Immunohistochemical scoring of the stages was done according to the membranous and cytoplasmic staining. The following scoring system is concordant to the literature (10): ≤ 5% positive cells-score 0, 6%-25% positive cells-score 1, 26%-50% positive cells-score 2, > 51% positive cells were designated as score 3.
All of the data were statistically analyzed with SPSS (Statistical Packages for Social Sciences) program using Mann Whitney U, Chi-Square, Wilcoxon and variation analysis tests. Probability of < 0.05 was considered significant.

Results

Mean age of patients was calculated using Mann Whitney U test. Mean age was 62.2 ± 20.2 years in invasive bladder cancer group and 65.2 ± 16.7 years in superficial bladder cancer group. There was no significant mean age difference between these groups ($p > 0.05$). Mean age of all patients was calculated as 64.07 years (Table 1).
Gender of patients were compared by using Fischer test showing no significant difference between invasive and superficial bladder cancer groups ($p > 0.05$) (Table 2).
Tumor and normal (control) tissue samples were compared for EMMPRIN, p65, p38 immunostaining in the invasive group using Wilcoxon test. All the tumor tissues were stained positively compared to the controls with these markers and it was statistically significant ($p < 0.05$). Applying this same method to the superficial group, we also found that superficial bladder tumor samples were stained positively with all of the markers, compared to the controls ($p < 0.05$) (Table 3).

Table 1.

Age analysis of the patients.

	Group	n	Youngest	Oldest	Mean	Standard Deviation	p
Age	All patients	91	30	84	64,07	10,363	
	Invasive	34	43	79	62,2	8,051	0,135
	Superficial	57	30	84	65,2	11,443	

Table 2.

Gender analysis of the patients.

		Male	Female	Total	p
Invasive	n	31	3	34	0,357
	%	91,2%	8,8%	100%	
Superficial	n	47	10	57	
	%	82,5%	17,5%	100%	
Total	n	78	13	91	
	%	85,7%	14,3%	100%	

taining between pTa and pT1 bladder tumors ($p > 0.05$) and no difference between pTa and pT1 superficial bladder tumors for p38 and EMMPRIN immunostaining ($p > 0.05$). Briefly, no relation between marker expressions and superficial tumor stages was found. When we compared antibody expressions and stages of invasive bladder cancer patients, we found similar results as the superficial group. There was no relation between pT2, pT3, pT4 stages and antibody expressions ($p > 0.05$) (Table 4). Next, tumor grades and marker expressions were compared. G1 tumours were excluded from statistical analysis because we observed them in only 6 patients with superficial bladder tumors. p65 expressions were indifferent in G2 and G3 invasive and superficial bladder cancers ($p > 0.05$). p38 expressions in G2 tumors were found to be higher in the invasive group compared to the superficial group ($p < 0.05$) and this higher p38 expressions was also observed in G3 invasive tumors ($p < 0.05$). EMMPRIN had a more positive staining in G2 invasive tumors compared to the superficial tumors of the same grade ($p < 0.05$). But this more positive staining for EMMPRIN in invasive tumors was not confirmed in G3 tumors ($p > 0.05$) (Table 5-8).

Table 3.

Tumor-control group comparison based on antibody positivity in invasive and superficial bladder tumors.

	INVASIVE			SUPERFICIAL		
Immunostaining	**Antibody positivity**	**n**	**p**	**Antibody positivity**	**n**	**p**
p65	Tumor p65 < Control p65	0	**0,000**	Tumor p65 < Control p65	0	**0,000**
	Tumor p65 > Control p65	32		Tumor p65 > Control p65	53	
	Tumor p65 = Control p65	2		Tumor p65 = Control p65	4	
	Total	34		Total	57	
p38	Tumor p38 < Control p38	0	**0,000**	Tumor p38 < Control p38	0	**0,000**
	Tumor p38 > Control p38	0		Tumor p38 > Control p38	49	
	Tumor p38 = Control p38	17		Tumor p38 = Control p38	8	
	Total	34		Total	57	
EMMPRIN	Tumor Emmprin < control EMMPRIN	0	**0,009**	Tumor Emmprin < control EMMPRIN	0	**0,034**
	Tumor Emmprin > Control EMMPRIN	8		Tumor Emmprin > Control EMMPRIN	5	
	Tumor Emmprin = Control EMMPRIN	26		Tumor Emmprin = Control EMMPRIN	52	
	Total	34		Total	57	

Table 4.

Antibody positivity comparison among invasive bladder tumors.

		p65	p38	EMMPRIN
Tumor stage		**p**	**p**	**p**
pT2	pT3	0,78	0,24	0,39
	pT4	0,58	0,81	0,66
pT3	pT2	0,78	0,24	0,39
	pT4	0,28	0,69	0,96
pT4	pT2	0,58	0,81	0,66
	pT3	0,28	0,69	0,96

Grades of invasive and superficial bladder tumors were compared by chi square and Mann Whitney U tests. Tumor grades were found higher in the invasive group ($p < 0.05$). There was no significant difference for p65 immunos-

Discussion

p38MAPK expression in tumor tissues was higher than normal tissues and this situation may result from increased intracellular activities such as proliferation, differentiation, cell cycle regulation, apoptosis; which are

Table 5.

Mean antibody positivity in invasive and superficial Grade 2 bladder tumors.

	Group	N	Mean	Std. deviation	Std. error mean
Age	Invasive	7	58,14	9,353	3,535
	Superficial	38	65,24	12,510	2,029
p65	Invasive	7	2,00	,816	,309
	Superficial	38	2,24	,714	,116
p38	Invasive	7	1,26	,535	,202
	Superficial	38	,57	,601	,098
EMMPRIN	Invasive	7	,71	,951	,360
	Superficial	38	,13	,414	,067

Group statistics

Table 6.

Comparison of all antibodies in Grade 2 invasive and superficial bladder tumors. Test Statistics [b]

	Age	p65	p38	EMMPRIN
Mann-Whitney U	83,000	110,500	61,000	87,500
Wilcoxon W	111,000	138,500	89,000	828,500
Z	-1,568	-,763	-2,657	-2,261
Asymp. Sig. (2-tailed)	,117	,446	**,008**	**,024**
Exact Sig. [2*(1-tailed Sig.)]	,123a	,489 [a]	**,023** [a]	,157 [a]

[a] Not corrected for ties.
[b] Grouping variable: grup.

Table 7.

Mean antibody positivity in invasive and superficial Grade 3 bladder tumors.

	Group	N	Mean rank	Sum of ranks
Age	Invasive	27	20,50	553,50
	Superficial	13	20,50	266,50
	Total	40		
p65	Invasive	27	19,20	518,50
	Superficial	13	23,19	301,50
	Total	40		
p38	Invasive	27	27,58	461,50
	Superficial	13	17,09	358,50
	Total	40		
EMMPRIN	Invasive	27	21,22	573,00
	Superficial	13	19,00	247,00
	Total	40		

Table 8.

Comparison of all antibodies in Grade 3 invasive and superficial bladder tumors. Test statistics [b]

	Age	p65	p38	EMMPRIN
Mann-Whitney U	175,500	140,500	83,500	156,000
Wilcoxon W	266,500	518,500	461,500	247,000
Z	,000	-1,110	-2,884	-,909
Asymp. Sig. (2-tailed)	1,000	,267	**,004**	,364
Exact Sig. [2*(1-tailed Sig.)]	1,000 [a]	,317 [a]	**,007** [a]	,588 [a]

[a] Not corrected for ties.
[b] Grouping variable: grup.

the cell responses to oxidative stress, inflammatory cytokines, mutagens and growth factors. Human colon carcinoma cells have an increased activity on MAPK pathway (11). In our study, the expression of p38 was higher in invasive bladder cancer than superficial bladder cancer. Increased p38 expression may be due to difference of local invasion between the groups and this situation was also found in a study about the local invasiveness of breast cancer cells (12). MAPK is also active in motility and invasiveness of hepatocellular carcinoma (13). Inhibition of MAPK pathway by cytokine suppressive drugs was shown to disrupt the secretion of proteolytic enzymes in malignant melanoma cells and thereby decreasing tumor invasiveness (14). Breast cancer cells may proliferate and invade surrounding areas by activating MAPK pathway in the absence of growth factors (15). Aurora A gene over expression which is a target antibody for MAPK was detected by mRNA extraction with polymerase chain reaction (PCR) and immunostaining in bladder cancer tissue samples. This antibody is thought to increase the risk of progression and metastasis in bladder cancer (16).

As previously noted about NFkB, this pathway functions in cell survival under various extracellular stimuli. Inhibition of NFkB pathway attenuates primary tumor invasive potential (17). In our study tumor samples were stained positively compared to the controls but this immunostaining occurred without relation to tumor grade and stage. *Kontos et al.* (18) published an article about 140 bladder cancer patients whose tumor samples stained positively with p65. Antibody expression was correlated with tumor grade but not stage. In a study performed with cell culture macrophages attached with ovarian or breast cancer, cell lines secreted TNF (tumor necrosis factor) alpha and invaded epithelium with the help of NFkB activation (19). In the same study macrophages in the noncancerous cell line didn't invade through epithelium. PDGF (platelet derived growth factor) increased DNA-NFkB binding and helped the invasion of breast cancer cells like TNF alpha (20). When IKBA -an inhibitor of NFkB pathway- had a defect, it was shown that gastric carcinoma progressed more aggressively (21).

EMMPRIN expression was detected in 60-100% of squamous cancers, 87% of pancreatic cancers, 83% of chromophobe renal cell carcinomas, 83% of hepatocellular carcinomas, 83% of medullary breast cancers, 79% of adenocarcinomas and glioblastoma multiformes (22).

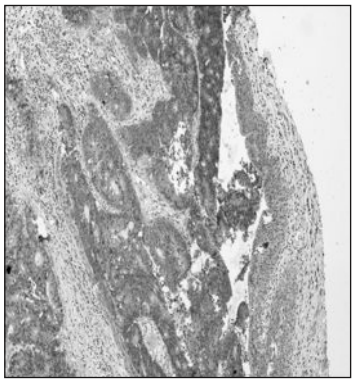

Figure 1.
Score 2 immunohistochemical staining with EMMPRIN in invasive bladder tumor (Magnification 100x).

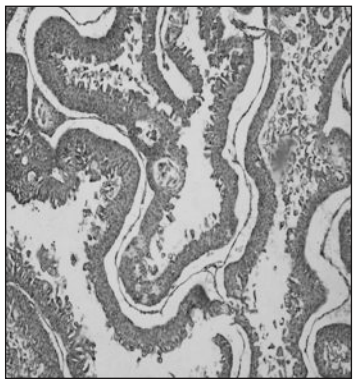

Figure 2.
Score 2 immunohistochemical staining with)p38 in pT1G3 superficial bladder tumor (Magnification 100x).

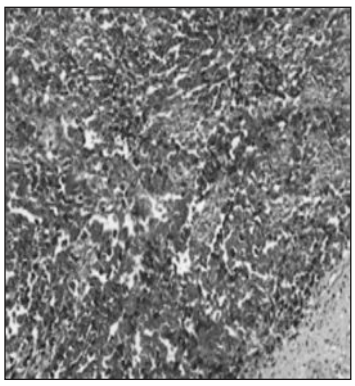

Figure 3.
Score 3 immunohistochemical staining with p65 in Grade 3 superficial bladder tumor with squamous differentiation (Magnification 100x).

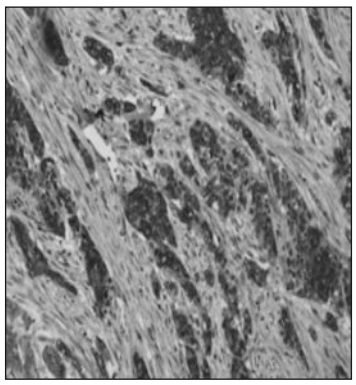

Figure 4.
Score 3 immunohistochemical staining with p65 in in Grade 3 superficial bladder tumor with squamous differentiation (Magnification 100x).

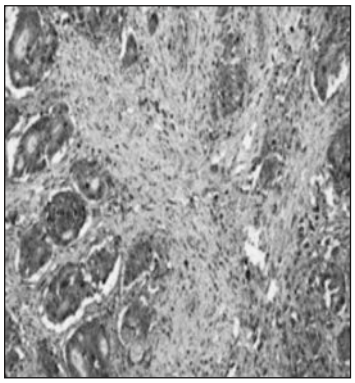

Figure 5.
Score 2 immunohistochemical staining with p65 in invasive bladder tumor (Magnification 100x).

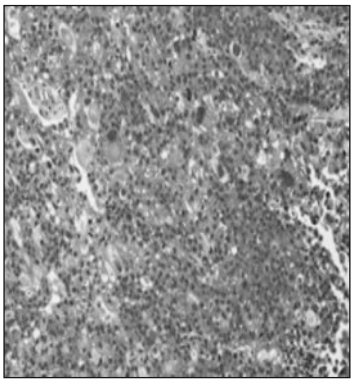

Figure 6.
Score 2 immunohistochemical staining with p38 n p T1G3 papillary urothelial carcinoma of the bladder (Magnification 100x).

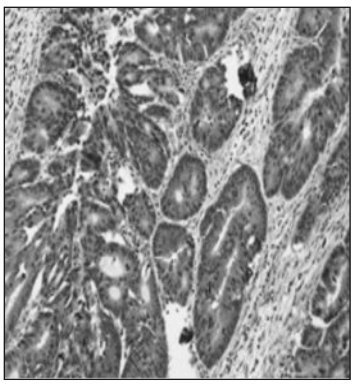

Figure 7.
Score 1 immunohistochemical staining with p38 in invasive bladder tumor (Magnification 100x).

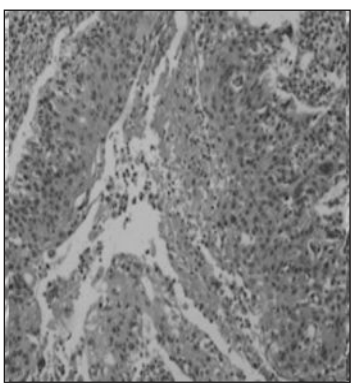

Figure 8.
Score 0-1 immunohistochemical staining with p38 in pure differentiated bladder tumor (Magnification 100x).

In addition to EMMPRIN's extracellular matrix degradation effect, it has a role in angiogenesis of tumor tissue and chemoresistance (23). EMMPRIN which is expressed on cell membranes of drug resistant tumor cells (24), induces chemoresistance and invasion in hepatocellular carcinoma (25).

In our study, EMMPRIN expression was positive in tumors when compared to the normal tissue. This positivity was significantly different and more expressed in G2 invasive bladder cancers compared to the superficial G2 bladder tumors. EMMPRIN's increasing expression towards poorly differentiated tumors was also detected in thyroid carcino-

ma (26). EMMPRIN expression was directly related with Fuhrman grade in renal cell carcinomas and increased EMMPRIN expression was related with poor prognosis (27). EMMPRIN expression was more common among clear cell renal carcinoma and this subtype was associated with increased invasion and metastasis (28).
In an article about prostate cancer, EMMPRIN immunostaining was 82.3% in prostate cancer specimens but it was only 13.3% in benign prostate hyperplasia specimens (29). Our results about the comparison of tumor and controls are correlated with contemporary literature. Also in the aforementioned article EMMPRIN positivity was associated with higher Gleason scores and tumor stage which are also linked with poor patient outcome like in high Fuhrman grade renal cell carcinoma prognosis.
We observed that EMMPRIN expression was not correlated with the stage of the disease. In a study about 65 patients with invasive squamous cervix carcinoma, antibody expression was not different in FIGO (Federation Internationale de Gynecologie et d'Obstetrique) stage 1 and 2 tumors (30). In the same study poorly differentiated cervix carcinomas were associated with higher EMMPRIN expression simirarly to our results.
p38MAPK and EMMPRIN coexpression was found in our study. Although the exact relation between them is not fully understood, it is known that under external stimuli normal cells give an inflammatory response and tumor cells show invasion and metastasis. For instance MMP-2 induction is shown to act by MAPK activation in malignant melanoma (31). Also p38 phosphorylation increases MMP-9 expression in serous ovarian cancer and EMMPRIN is the main inducer for MMP-9 (32). Our results about coexpression is correlated with recent knowledge.
Our study is the first one in the literature about p38, p65 and EMMPRIN expression comparisons in both invasive and superficial bladder cancers. We hope that further data will better explain the invasion/metastasis pathophysiology, the mechanism of action of new chemotheraupetic drugs and the prognosis of bladder cancer patients in the future.

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ORIGINAL PAPER

Analysis of survival in radical and postoperative radiotherapy for prostate cancer

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Summary

Purpose: *To analyze survival and complications in high dose 3D conformal radiotherapy (3DCRT) patients treated with curative and post-operative intent and compare radical surgery + radiotherapy (RT) patients vs. RT only patients.*

Material and method: *103 patients were treated curatively (RAD), 94 postoperatively (POST-OP). The mean age was higher in RAD group (72.6 years, range 56.4-85.1) than in POST-OP group (65.4 years, 43.9-77) ($p < 0.0001$). According to NCCN prognostic classification 13 (12%) patients was low risk, 48 (47%) intermediate risk and 42 (41%) high risk in RAD group. In POST-OP group 13 (14%) patients were low risk, 37 (40%) intermediate risk and 44 (46%) high risk. Hormone Therapy (HT) was administered in 98 patients (95%) in RAD and in 45 patients (47.8%) in POST-OP. Patients were treated with a three-dimensional conformal radiotherapy (3D-CRT). In RAD 15 (15%) were alive with disease (AWD), 5 (5%) dead of disease (DOD) and 10 (10%) dead of other cause (DOC); in POST-OP 14 (14.8%) were AWD, 2 (2%) DOD and 3 (3%) DOC. The prescription dose was 80 Gy in 2-Gy fractions in the RAD group, and 70 Gy in 2-Gy fractions in the POST-OP, respectively.*

Results: *No biochemical or clinical relapse was found in low risk patients in RAD group and 1 relapse in POST-OP group. The largest number of relapses occurred and in intermediate-high risk in RAD (39%) and POST-OP group (33%). In the cause-specific survival analysis no significant differences were found in high risk group between RAD and POST-OP ($p = 0.9$). In the biochemical relapse-free survival (bRFS) at 5 years analysis no significant differences were found in the high risk group between RAD and POST-OP ($p = 0.1020$).*

Conclusion: *RT in RAD low- risk is very effectiva. RAD and POST-OP RT were well tolerated with a very low toxicity. The cause-specific survival at 5 years was 95% and 97% for the two groups of treatment, RAD and POST-OP respectively (Log-rank test $p = 0.2908$).*

KEY WORDS: *3D conformal radiotherapy; Surgery; High risk prostate cancer; Late toxicity.*

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INTRODUCTION

In the present report, we analyzed and compared the results of high dose three dimensional conformal RT (3DCRT) in radical or post-operative setting in patients consecutively treated for clinically localized prostate cancer. The prostate cancer (CaP) is the most common malignancy found in males. With the diffusion of prostatic-specific antigen (PSA) screening, patients are more likely to be diagnosed with earlier stage disease. According to the *National Comprensive Cancer Network* (NCCN), localized CaP is defined by the absence of nodal or distant metastases: low, intermediate and high risk. Locally advanced tumors (very high-risk) include T3b-T4 N0 M0 cases, whereas N1 and/or M1 patients are considered metastatic (1). Histology is associated with the natural history and prognosis of patients with prostate cancer. The Gleason score is determined by evaluating the glandular architecture of the cancer. Treatment choice is based on the well-established prognostic factors: clinical stage, initial PSA level and Gleason score. Several risk group definitions by *D'Amico et al.* (2) and those defined by NCCN found wide

application. In addition, other factors, may influence prognosis: nadir PSA at 12 months, PSA doubling time, age and radiotherapy dose (3).
Standard treatments for CaP include radical prostatectomy (RP), radiotherapy (RT), hormonal therapy (HT) and observation. Radical radiotherapy can be offered to patients with localized and locally advanced disease (4, 5) Three recent prospective randomised-controlled studies (5-7) based on multiple retrospective series (8-11) indicated that adjuvant RT in patients with risk factors for local residual disease results in longer biochemical relapse-free survival (bRFS) and a longer time to clinical failure when compared with patients managed expectantly. A rise by 2 ng/mL or more above the nadir PSA must be considered the standard definition for biochemical failure after RT with or without HT (13). In POST-OP biochemical failure is defined as increased PSA values > 0.2 ng/ml (42). Recent retrospective analysis compare the results of radical surgery vs. a conservative approach such as external beam RT plus HT and showed a significantly better outcome after RT than after RP alone in patients with high-risk prostate cancer (14). High dose schedules have clearly shown a dose-response effect in terms of improvement of bRFS (15). We analyzed and compared in according to NCCN pre-treatment definition.

Materials and Methods

197 patients with clinically localized prostate cancer referred at RT department of our Hospital were analyzed retrospectively. 103 patients underwent radical radiotherapy (RAD group) ± androgen deprivation therapy; 94 patients with undetectable PSA levels and adverse pathologic factors after radical retropubic prostatectomy underwent postoperative RT (POST-OP group) ± androgen deprivation therapy. The primary endpoints were biochemical disease free survival and late toxicity outcome. The mean follow-up was 56.7 months (4.6 years); standard deviation (DS) 17.8 months, median 59.2 months (4.86 years); min/max 6.8/96.1 months (0.56/7.9 years).
Patients characteristics are shown in Table 1. The mean age was higher in RAD group: 72.6 years (range 56.4-85.1, median 73.8) for RAD group and 65.4 years (range 43.9-77, median 65.3) for POST-OP group ($p < 0.0001$). In RAD 65% were Gleason 2-6, in POST-OP 50% Gleason 2-6. Patients were stratified into the risk groups according to a pre-treatment defined NCCN (1) definition.
HT was used in 98 patients (95%) in RAD and 45 patients (47.8%) in POST-OP. Other HT patients characteristics are shown in Table 2. The choice of HT was left at physician decision, and it consisted in the administration of LHRH analogues, anti-androgen or both. Mean duration of HT was ≤ 6 months for 66% and 64% of patients in the RAD and POST-OP group, respectively.
Dose prescribed was 80 Gy for RAD patients and 70 Gy for POST-OP patients (18-21).
In the RAD group, failure was defined as a serum PSA level at nadir more than 2 ng/mL (42). For the POSTOP group, failure was defined as a PSA level > 0.2 ng/mL (13). The interval to BF was defined as the time from the beginning of RT/RP to the cutoff point.
All patients were clinically evaluated for urinary and rec-

Table 1.
Patient characteristics.
Age confidence interval p < 0.0001.

Patient characteristics	RADICAL	POST-OP
N	103	94
%	48%	44%
Age mean	72,6	65,4
Age D.S.	5,7	6,7
Age median	73,8	65,3
Age min	56,4	43,9
Age max	85,1	77
Age confidence interval min	71,493	64,029
Age confidence interval max	73,706	66,802
Gleason score		
2-6	67 (65%)	26 (50%)
7	13 (13%)	10 (19%)
8-10	21 (21%)	16 (31%)
PSA		
Mean	20,1	18,2
D.S.	27,9	26
Median	12	9
Min	1	3,8
Max	210	185
NCCN prognostic group		
Low	13 (12%)	13 (14%)
Intermediate	48 (47%)	37 (40%)
High	42 (41%)	44 (46%)
Very high	1 (1%)	29 (31%)

Table 2.
Hormonotherapy.

Hormone therapy	HT RADICAL		HT POST-OP	
Mean	10 months		14 months	
D.S.	15 months		20 months	
Median	6 months		6 months	
Min	1 month		1 month	
Max	84 months		71 months	
HT	n. 98	95%	n. 45	48%
NO HT	n. 5	5%	n. 49	52%
HT </= 6 months	n. 57	66%	n. 18	64%
HT >/= 7 months	n. 30	35%	n. 10	36%
HT peripheral	n. 32	31%	n. 35	37%
HT LH-RH	n. 10	10%	n. 6	6%
HT TAD	n. 56	54%	n. 12	13%
HT before RT	n. 30	29%	n. 62	66%
HT before and during RT	n. 20	19%	n. 6	6%
HT before during and after RT	n. 53	52%	n. 26	28

tal complications according to RTOG acute effect and RTOG/EORTC late effects score (22) and common toxicity criteria (NCI CTC Version 2.0) (23). Follow-up evaluation after treatments were performed at intervals of 3, 6 to 12 months with PSA measurement, clinical examination, abdominal-pelvic ultrasound and in some patients periodical TC, RM, PET, bone scan.

Statistical analysis

Data are expressed as means ± standard deviation. Differences in non-continuous variables were tested by χ^2 analysis. Differences between the means of the 2 continuous variables were evaluated by the Student's t test. Regression analysis with Pearson's test was also used to evaluate the relationship between the 2 continuous variables. Survival analyses were carried out (LIFETEST SAS procedure using Kaplan-Meier method, PROC GPLOT was used to graph the Kaplan-Meier estimates). The level of significance set at $p < 0.05$ was considered for all statistical analyses. Statistical analysis was performed using the SAS statistical software (SAS Institute Inc, Cary, NC) versions 8.2 for Microsoft Windows.

Results

The analysis involved 197 patient, 103 in the RAD group and 94 in the POST-OP group. The characteristics of the patients in the two treatment groups are reported in Table 1. Biochemical relapse using the ASTRO (12), Phoenix sistem (13) and PSA > 0.2 ng/ml (42) are shown in Table 3. The possible influence on bRFS of the continued androgen suppression in the HT patients was excluded, given the mean duration of HT of ≤ 6 months in 2/3 of the patients in both groups. Therefore we assumed that the possibility that these patients were still hypogonadal at their last PSA reading, was small, because the median follow-up for these patients (median 59.2) is significantly higher than median time for testosterone recovery (42, 43). Despite the retrospective comparison, patients in both groups were equally balanced according the NCCN guidelines (Table 1). This was confirmed by the non-significant differences between the bRFS curves for the different risk group, reported in Table 3. In RAD seventy-three (70.9%) patients had no evidence of disease (NED), 15 (14.5%) were alive with disease (AWD), 5 (4.8%) dead of disease (DOD) and 10 (9.7%) dead of other cause (DOC) and in POST-OP 75 (79.8%) were NED, 14 (14.9%) AWD, 2 (2%) DOD and 3 (3.2%) DOC (Table 3). The overall survival at 5 years was 86% in RAD and 94% in POST-OP. The cause-specific survival at 5 years was 95% and 97% for two group of treatment, RAD and POST-OP respectively (Log-rank test p = 0.2908) (Figure 1). In the bRFS analysis no significant differences were found in high risk group between RAD and POST-OP p = 0.1020 (Figure 2). Survival stratified by age group was not statistically significant. In the bRFS analysis no significant differences (p = 0.6) were found for the low, intermediate and high risk between RAD and POST-OP group. The cause-specific survival in the high risk patients, according to the duration of HT, didn't show statistically significant difference in the RAD or POST-OP, whereas statistically significant difference was found for type of HT but only in RAD (LH-RH 100% -> TAD 96% -> peripheral 67%) (P = 0.0594).
Multivariate analysis of cause-specific survival for age, NCCN, HT, PTV volume, HT months showed difference only for age (p = 0.0699) and NCCN (p = 0.0156) in RAD but without statistically significance; none difference in POST-OP; no significant difference for other indicators.
Analyzing adverse histopathologic findings after RP, emerged a subgroup in POST-OP which could have a trend towards an higher risk of biochemical recurrence, which was the positive capsular involvment (p = 0.15). In RAD patients we applied the formula for *Roach/Vargas* (24) and the risk groups < 15 (60%), 15-30 (21%), > 30 (17%) were

Table 3.
Recurrence and status of life.

Biochemical falilure PSA Nadir + 2 ng/ml	**RADICAL**	**POST-OP**
Low	0	0
Intermediate	2 (4.2%)	3 (8.1%)
High	14 (35%)	3 (7%)
Tot	16 (16%)	6 (6.4%)
biochemical falilure 3 consecutive PSA rises	**RADICAL**	**POST-OP**
Low	0	0
Intermediate	3 (6.4%)	6 (16.2%)
High	15 (37.5%)	5 (11.6%)
Tot	18 (17%)	11 (11.8%)
Biochemical falilure PSA > 0,2 ng/ml	**RADICAL**	**POST-OP**
Low		1 (7.7%)
Intermediate		6 (16.2%)
High		7 (16.3%)
Tot		14 (15%)
Metastases	**RADICAL**	**POST-OP**
Low	0	0
Intermediate	2 (4.2%)	0
High	7 (17.5%)	2 (5.4%)
Tot	9 (9%)	2 (2%)
Status of life	**RADICAL**	**POST-OP**
No evidence of disease (NED)	73 (71%)	75 (79%)
Alive with disease (AWD)	15 (15%)	14 (15%)
Dead of disease (DOD)	5 (5%)	2 (2%)
Dead other cause (DOC)	10 (10%)	3 (3%)

Table 4.
RTOG/EORTC late toxicity.

POST-OP		**RAD**	
GU	**GI**	**GU**	**GI**
G0 = 51 (54.3%)	G0 = 68 (72.3%)	G0 = 58 (56.3%)	G0 = 74 (71.1%)
G1 = 15 (16%)	G1 = 7 (7.4%)	G1 = 19 (18.3%)	G1 = 14 (13.4%)
G2 = 4 (4.2%)	G2 = 5 (5.3%)	G2 = 13 (12.5%)	G2 = 7 (6.7%)
G3 = 10 (10.6%)	G3 = 1 (1%)	G3 = 7 (6.7%)	G3 = 0
G4 = 0	G4 = 0	G4 = 0	G4 = 0

Figure 1.
Cause-specific survival – p = 0.2908.

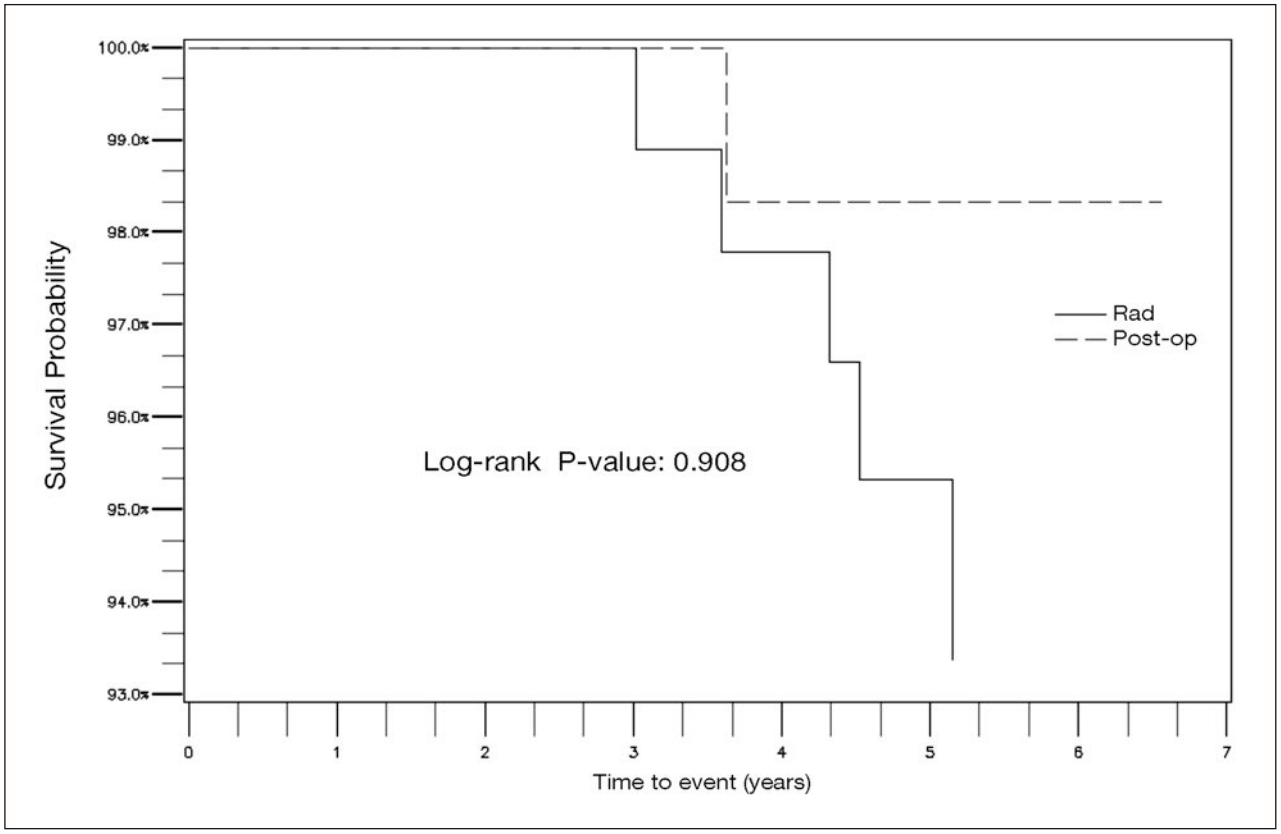


Figure 2.
High risk disease free survival – p = 0.1020.

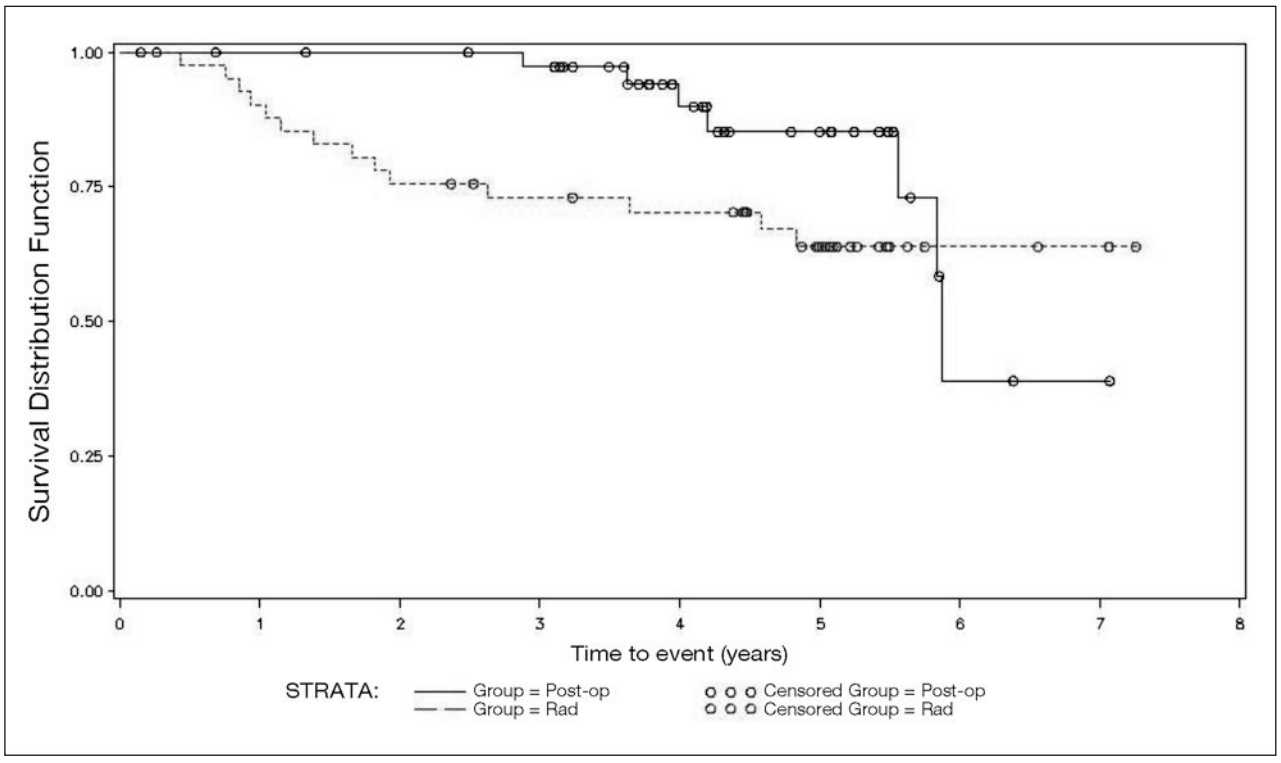
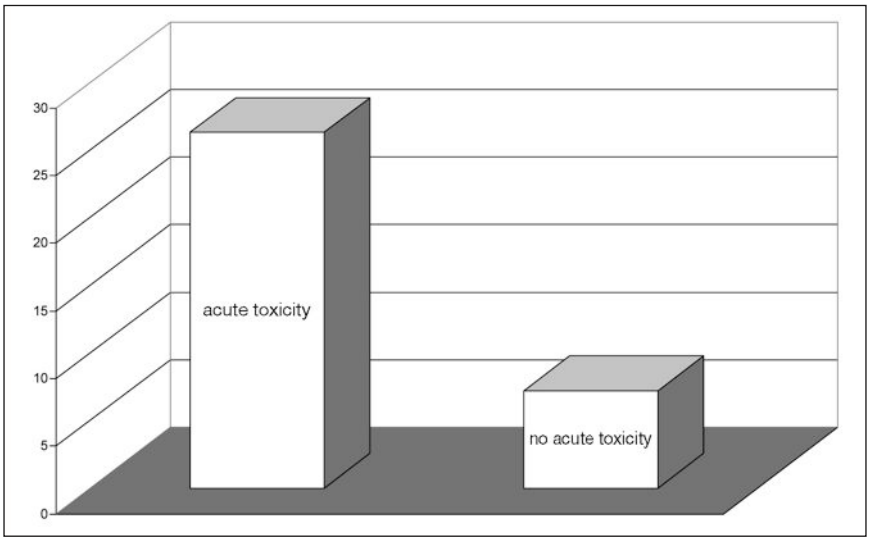


Figure 3.
Incidence late toxicity.



found strongly correlated to the bRFS (p = 0.0039). Although pelvic node were not irradiated, only 2 lymph node metastases occurred (cT2aN0, Gleason 9, PSA 51; cT2N0, Gleason 8, PSA 21). Analysis of gastrointestinal (GI) late toxicity showed 7 (6.7%) G2 patients in RAD, 5 (5.3%) patients in POST-OP. One patients (1%) developed G3 proctitis in POST-OP. No patients G3 in RAD. Genitourinary (GU) late toxicity grade G2 were observed in 13 (12.5%) patients in RAD, and 4 (4.2%) patients in POST-OP. G3 GU late toxicity occurred in 7 patients (6.7%) in RAD and in 10 patients (10.6%) in POST-OP. No patients lately developed a grade 4 GI and GU toxicity (Table 4). Grade 3 toxicity was observed as urethral strictures and was corrected with transurethral dilatation or resection (TURP). Urinary control was evaluated before and after RT. As expected problem with urinary incontinence were more frequent among patients treated by radical prostatectomy. G4 pre-irradiation and post-irradiation incontinence was absent in both groups, G2-G3 pre irradiation incontinence was reported in 10 patient (17.5%) in POST-OP, no patients in RAD. After RT G2-G3 incontinence was reported in 3 patients (5.2%) in RAD and 18 (25.4%) in POST-OP group. Late G3 GI and GU toxicity were analyzed for possible relationship with some treatment parameters. Greater toxicity was recorded in patients with higher PTV volume without statistical significance (p = 0.1878). Among patients who had developed acute symptoms during treatment, the incidence of late toxicity of all grade at 10 years was 26.3%, compared with 7.2% (p = 0.0053) of all patients without acute toxicity (Figure 3). The analysis of cardiac event showed in RAD none patient, in POST-OP 3 G1-G2 events (3.2%); G3: 1 (4.2%); G4: 1 (4.2%).

Discussion

It is generally accepted that low RT doses are inadeguate to control CaP for curative intent and dose-escalation studies have been pubblished on this topic. *Zietman* (25, 30) compared 70.2 Gy versus 79.2 Gy 3DCRT in stage T1-T3, *Pollack* (26, 30) compared 70 Gy versus 78 Gy, and *Kupelian* (27, 30) dose under and over 72 Gy: the results of all these studies confirmed that higher doses are necessary to control CaP and the effect of increasing the dose has obtained better biochemical failure rates. *Zelefsky* (28, 30) in dose escalation study from 64.8 to 86.4 Gy showed an advantage on biochemical relapse-free survival rate (bRFS) with doses over 75.6 Gy in intermediate risk group patients and with doses of 81 Gy in high risk group patients (67% versus 43%) and also the data suggested that some patients could benefit from doses over 80 Gy. *Kupelian* (27, 32, 35) confirmed the benefit of greater radiation doses not only to obtain better local control but also on distant metastases (29, 30). In our work, independently from prognostic status NCCN, we delivered total doses of 80 Gy (2 Gy/fraction) for radical intent. Clinical target volume (CTV) included prostate and seminal vesicles independently from involvement of seminal vesicles and other adverse histopathologic findings.

In the bRFS analysis no significant differences were found for the low, intermediate and high risk group between RAD and POST-OP. Nevertheless high dose RT, the analysis of late toxicity showed low frequency and well tolerated treatment. In fact RAD GU late toxicity grade G3 showed 5.8% patients, whereas GI late toxicity grade G3 occurred in only one patient (subsequently evaluated, this patient presented a very high PTV volume). Randomized studies have not tested adjuvant RT versus close watchful waiting with early salvage of patients in whom a biochemical recurrence is detected by ultra-sensitive PSA assays (31). The European organization for research and treatment of cancer (EORTC) trial assessed the role of immediate postoperative radiotherapy after RP. The trial including 1005 patients with positive surgical margins or pT3 tumor showed that immediate RT improves biochemical progression-free survival and locoregional control compared to wait-and-see policy (5). Recently the data published by *Cozzarini* (32) provides strong support for the use of high radiation doses, >/= 70.2 Gy in the early postoperative irradiation of patients with undetectable PSA levels after RP fop CaP, and for the radiobiologic model postulating a 3% proportional gain of 5-year bRFS per incremental Gray in the postoperative setting (32).

GI G3 late toxicity in POST-OP was 7.4% with no GU G3 late toxicity. Incontinence G2-G3 post RT was infrequent in RAD, whereas in POST-OP raised from 7.4% (pre-RT) to 15% (post-RT). This date showed that the incontinence was more related to a previous surgery than to high dose RT. There was more GU toxicity than GI especially in RAD respect in POST-OP certainly in relation to greater dose delivered. The presence of acute toxicity had a significant

influence on the long-term development of GU and GI late toxicity (33). Infact among patients who had developed acute symptoms during treatment, the incidence of late toxicity at 10 years was 26.3%, compared with 7.2% (p = 0.0053) of all patients without acute toxicity. Furthermore, patients who had an increased treatment time had more late side effects. In CaP the regional lymph nodes are treated to prevent occult metastases, but most of the studies published were retrospective and conducted before the PSA advent. To identify patients that will benefit of pelvic nodes irradiation (PNI) the risk of lymph node involvement has been studied and validated by using the Partin table (34) or more recently Roach/Vargas formula (25). Recently for high and very high risk CaP data of the RTOG 94-13 (35) trial have demonstrated the role of PNI. On the contrary preliminary results of the GETUG-01 (36) trial did not show any benefit for PNI. PNI was performed in RAD when the patients was at high risk nodal involvement but the analysis of our data showed no clear benefit. Considering risk group with 15-30 and > 30 Roach score (25) the two nodal recurrence detected represent only 5% (2/38). Two randomized studies (38, 37) have indicated a survival benefit with the use of long term (≥ 2 years) rather than short-term (≤ 6 months) HT. As a result of these randomized data, long-term HT is commonly prescribed especially in high-risk CaP patients treated with RT. However, recent outcomes with dose escalation have indicated significant improvements compared with the lower doses (≤ 70 Gy) of RT used in the major HT trials. The improvements in RT delivery, make the benefit of long-term HT less certain in the contemporary era. Considered in conjunction with the results of studies indicating the negative effects of short- or long-term HT on bone, muscle, and cardiovascular health, and the high RT doses in our study, HT was used with a mean duration ≤ 6 months for 66% and 64% of the patients in the RAD and POST-OP group, respectively. We expected that HT and age could also have an impact on cardiac events (39-41), but none of them was observed although a longer follow-up would be desirable. *Arcangeli G et al.* (15) in recent retrospective analysis showed a not significantly different outcome after RT than after RP alone in patients with high-risk prostate cancer.
Our study we showed high bBFS comparable with that of *Cozzarini* (32) and higher than that of *Bolla* (5).
Furthemore RAD low risk group had a very good outcome. In POST-OP there is no difference between intermediate and high risk. Despite high doses of both, RAD and POST-OP RT were well tolerated with a very low toxicity.

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CASE REPORT

Regular ultrasound examination of transplanted kidneys allows early diagnosis of renal cell carcinoma and conservative nephron sparing surgery

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Summary

Introduction: *The development of malignancies is a relevant long-term complication of organ transplantation. Carcinoma of native kidney accounts for up to 5% of all malignancies found in transplant recipients. Primary clear cell type renal cell carcinoma (RCC) usually arises in the native kidneys. Its occurrence in the renal allograft has been reported infrequently.*

Case presentation: *We report a rare case of de novo RCC in a kidney allograft in a 41 years-old woman. Routine ultrasonography denoted a poorly marginated hypoechoic mass at the inferior pole of transplanted organ, confirmed by computed tomography which showed a lesion of 32 mm in diameter with characteristic radiological signs of RCC. The patient underwent nephron sparing surgery (NSS). At histological examination the tumor was T1-T2, N0, M0 with negative margins. At five years after NSS no significant impairment of renal function or recurrence was observed.*

Conclusion: *Primary carcinomas of the kidney can be detected after transplantation in the native or transplanted kidney. According to the European Guidelines on the long-term management of kidney transplantation, all recipients should have regular ultrasonography of native and allograft kidneys to screen for cancer, which occurs at a much higher incidence in transplanted patients. NSS is a safe and efficient procedure for the treatment of RCC in renal graft, resulting in the preservation of renal function and in long-term cancer control.*

KEY WORDS: *Renal cell carcinoma; Renal transplantation; Neoplasm.*

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INTRODUCTION

Because of its effectiveness, its cost, and the quality of life that it ensures, renal transplantation is a primary treatment option for patients with end-stage renal failure (ESRD) (1). However, immunosuppressive therapy increases the incidence of post-transplantation cancer (2).

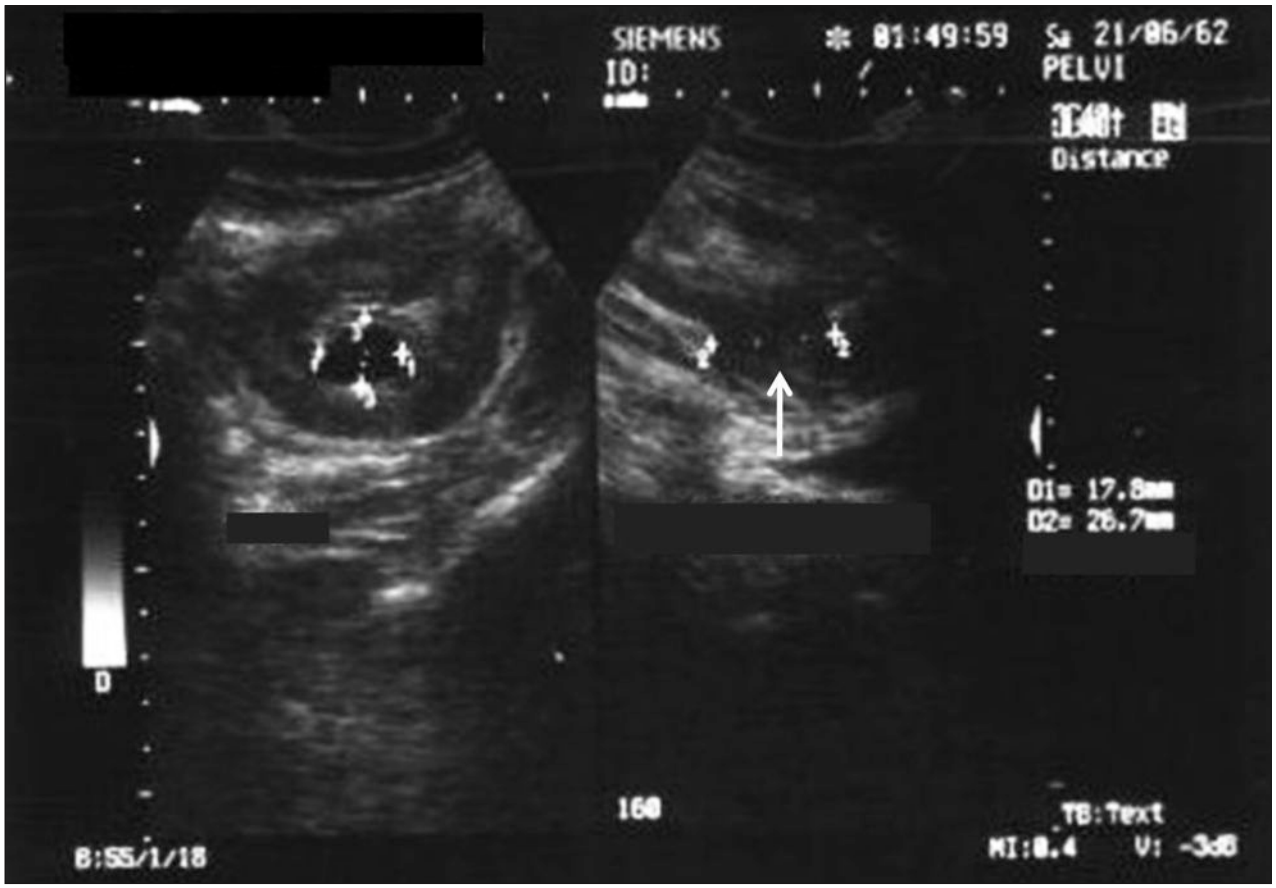
Incidence of renal cell carcinoma (RCC) in the general population accounts for 3% of all solid tumors (2). In kidney transplant recipients, incidence of RCC is similar to that of 20 to 30 years older subjects with normal renal function (2). RCC accounts for 4.6% of tumors in transplant recipients, 90% in native kidneys and 10% in the allograft (3). Considering the increase in donor age and in renal graft survival, nephrologists can expect to see an increase in the number of RCC cases in renal transplant recipients (4). Consequently, according to guidelines, renal transplant recipients must be screened with kidney graft ultrasound (US), in order to detect promptly a possible RCC (5).

The potentially worse prognosis of a RCC in immunosuppressed patients has motivated surgeons to perform graft removal as a first line treatment. Radical nephrectomy brings the patient back to dialysis treatment, significantly reducing life expectancy (6).

US screening of renal grafts allows early detection of small tumors, thus improving significantly the prognosis and allowing surgeons to perform nephron sparing sur-

Figure 1.

Inferior pole of the transplanted kidney; ultrasound shows a poorly marginated hypoechoic mass (arrow).



gery (NSS). The European guidelines for RCC (7) report that NSS is associated with a 10-year survival of 90% to 100% and a recurrence rate of 0% to 3%. In particular, NSS for RCC measuring less than 4 cm has the same results as radical nephrectomy, with a 10-year recurrence-free survival of 100% (7), making NSS the standard care for RCC less than 4 cm (7).

We report a case of de novo renal cell carcinoma in a kidney graft in which the early ultrasonographic diagnosis and the subsequent NSS played a key role to prolong graft survival and to uphold the patient's quality of life.

Case presentation

A 41 years-old woman developed ESRD from chronic glomerulonephritis of unknown etiology. After a short period of hemodialysis, she received a living donor kidney transplantation placed in the right pelvis from a 58-year old donor in 2001. Her immunosuppressive regimen included prednisone, tacrolimus, and mycophenolic acid. Routine follow-up examinations included chest x-rays and native kidneys and kidney graft US examination each year.

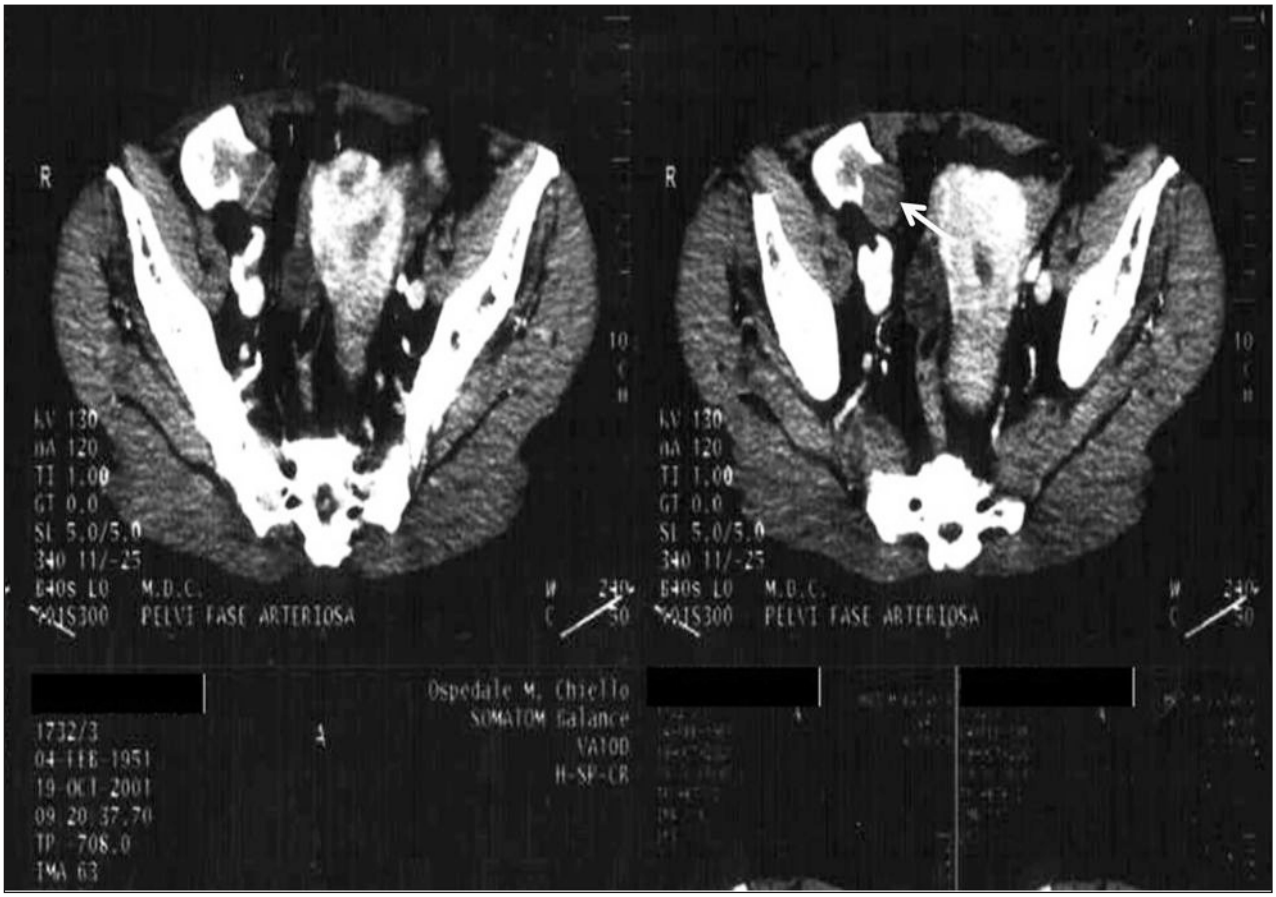
Five years after transplantation, renal function was normal (data from last 6 months: serum creatinine 1.0-1.3 mg/dL, blood urea nitrogen [BUN] 18-23 mg/dL, hemoglobin 11.6-12.4 g/dL, total leukocyte count 4980-6100/mm^3). At time of ultrasonography urine analysis showed 1+ albumin, 8-12 red blood cells and 15-20 leukocytes per high power field; urine culture was sterile; proteinuria was 150-200 mg/24H. Duplex US analysis of the native kidneys was unremarkable. Evaluation of the graft showed the kidney located deep within the right iliac fossa with normal dimensions (length 11.8 cm, width 4,8 cm), good differentiation of medulla and cortex with normal resistance index (RIs = 0.72-0.68-0.66). A poorly marginated, hypoechoic mass of 30.8 x 26.7 mm (Figure 1) was noted in the inferior pole of the graft. Abdominal computed tomography (CT) confirmed the presence of a 32 x 28 mm lesion in the lower pole of the transplanted kidney, showing a low and heterogeneous contrast-enhancement after contrast medium administration (Figure 2). Enlarged lymph nodes or metastases were not detectable.

After adequately informing the patient about alternative treatment strategies and the associated risks, she was treated with NSS. The mass was removed and postoperative recovery was uneventful.

Histopathological examination confirmed the diagnosis of a non invasive renal cell carcinoma T1-T2N0M0 papillary transitional cell carcinoma. The patient was discharged in good condition and her immunosuppressive

Table 2.

Computed tomography imaging shows, after contrast injection, a heterogeneous contrast-enhanced lesion (arrow).



therapy included prednisone, sirolimus and mycophenolic acid. At five years, her graft function remains unchanged after the NSS intervention.

Discussion

Post-transplant cancer, favored by immunosuppressive therapy, affects 3 to 7% of patients. The most frequent malignancies are lymphoproliferative disorders, such as B-cell non-Hodgkin's lymphomas, and skin carcinomas (8). RCC are responsible for 4.8% of post-transplant cancers compared with 3.0% in the general population (9). Most *de novo* RCC occur in the native kidney. Renal tumors may also develop in the allograft itself, but it is a rare event. *Chambade et al.* (4) reported 7 patients who developed RCC in the graft, among 2.050 patients, with an incidence of 0.39% comparable to 0.46% and 0.5% reported in two other published studies (10, 11). A significant increase in the number of RCCs in renal graft can be expected in the forthcoming years. Data from *National Italy Kidney Transplant Register* reported an increase in the median donor age between 2000 and 2006 (12). The percentage of donors 50 to 64 years old increased, as well as those older than 65 years that increased from 23.9% and from 32.8% (12). At the same time graft survival has increased and is now estimated to be 81.7% from 2000 to 2006 for adults recipients (12). These parallel increases bring the renal graft to an age comparable to the median age of RCC diagnosis in the general population.

There are no specific clinical features associated with renal carcinoma in transplant recipients. The most common clinical symptom of renal carcinoma is macroscopic hematuria, which can be a late manifestation of the disease. Regular US examination of the renal graft is therefore indicated, although even US diagnosis of urothelial malignancy can be difficult, especially when the lesions are small and when there is no dilatation of the collecting system.

RCC usually presents as a solid mass with an echogenicity similar to the renal cortex; less common features include disruption of a portion of the hilar complex with preservation of the surrounding renal parenchyma, and localized disruption of the parenchymal structure due to mass infiltration. Color Doppler can be useful for distinguishing a tumoral mass from blood clots in the collecting system.

The differential diagnosis of a soft tissue mass in the central complex includes a squamous cell carcinoma, metastasis and lymphoma. A strong limitations of US is that should not be used to exclude urothelial disease, especially when the collecting system is not dilated. Thus

renal US is the only tool confirmed as having value in the screening, allowing a noninvasive and inexpensive assessment and diagnosis of RCC in kidney transplant recipients.
CT and/or MRI can more specifically detect small lesions and they should be performed when US findings raise doubts. Moreover, graft evaluation by CT and/or MRI is necessary for tumor staging. While CT is the best current imaging modality overall for staging of upper urinary tract urothelial tumors, results obtained in low-stage tumors must be viewed with caution, particularly when precise preoperative clinical staging is essential to evaluate the feasibility of NSS.
Transitional cell carcinomas constitute at least 85% of primary urothelial neoplasms. Squamous cell carcinoma and papillary RCC occur less frequently (8). The standard surgical treatment for native kidney malignancies is radical nephrectomy, but when this approach is applied to the graft it brings the patient back to dialysis treatment (6). This could be avoided by adopting the NSS technique, provided that tumors are detected in the early stages by US.
Results of NSS reported for small RCC of renal grafts are excellent (4, 13), with only one case reported to return to hemodialysis after NSS (7). Alternatives to NSS, particularly in small size (< 20 mm) lesions, are percutaneous radiofrequency ablation (RFA) and cryoablation.
A few patients have already been successfully treated with percutaneous RFA for de novo RCC in the graft (1, 14, 15), but their follow-up was limited to three months. Cryoablation of a de novo RCC of the graft has also been reported (16) with interesting results, although not sufficient to avoid some concerns about long-term results of this technique.
On the other hand, the high risks of open partial nephrectomy in these patients a minimally invasive approach particularly attractive.
The modification of the immunosuppressive regimen for transplant recipients surgically treated for carcinoma is still a matter of debate. Unlike ciclosporin, rapamycin does not increase the risk of malignancy but on the contrary it decreases the risk of lymphoproliferative disorders (17-19). Importantly, mTOR regulates essential signal transduction pathways involved in cell cycle progression (18). To our knowledge, there are no published specific recommendations on the management of antirejection therapy for patients with de novo malignancies of the native or transplanted kidney. Furthermore, in transplant recipients, reduction or even interruption of antirejection treatment under nephrologic surveillance should be considered and discussed with the patient (15, 17-19).
We believe that a systematic US screening for kidney transplant recipients can better detect and prevent RCC in the graft. In the majority of transplant centers, annual CT o US check-up of the native kidneys, allograft and other organs are routinely performed in order to detect de novo malignancy post transplantation. Roupret et al [20] have recommended a yearly follow-up by US, which has the best performance in the screening (i.e., noninvasive and inexpensive assessment) of renal carcinoma in kidney transplant recipients (21).

Conclusion

RCC in a renal graft is a rare disease. Ultrasound of the renal graft performed on a regular basis seems to be an appropriate tool for the screening of RCC. When cancer is suspected after US screening, CT scan appears to be a critical step in the diagnostic process, determining the feasibility of NSS. In our case NSS for a small RCC of the renal graft was feasible and safe. It resulted in good long-term functional and oncological outcomes.
However, when a minimally invasive approach is not possible, radical nephrectomy is the treatment of choice. In the presence of metastatic disease, chemotherapy with adjustment or cessation of immunosuppressive therapy is required.
Our case confirms that systematic annual US evaluation of the kidney graft in renal transplant recipients is an effective approach to patient care.

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CASE REPORT

Solitary giant sarcomatoid carcinoma of the bladder. A case report

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Summary

A case of sarcomatoid carcinoma of the bladder (SCB) presenting as a giant intravesical mass in a 75-year-old man complaining of lower urinary tract swmptoms (LUTS), abdominal pain and fever is reported. SCB is a rare (0.1% of all primary bladder tumors), aggressive cancer with a complex histology (a biphasic tumor with malignant epithelial and mesenchymal elements) and poor prognosis.

KEY WORDS: Bladder sarcomatoid carcinoma; Bladder giant mass; Non urothelial bladder cancer; Rare bladder cancer.

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INTRODUCTION

The sarcomatoid carcinoma of the bladder (SCB) is a neoplasm accounting for approximately 0.1% of primary bladder tumors. In a recent literature review, *Wang et al.* (1) collected 221 cases of SCB; an additional case, in whom lower urinary tract symptoms (LUTS) and abdominal pain heralded the tumor, is reported herein.

CASE REPORT

A 75-year-old man was admitted for evaluation of dysuria, pollachiuria, lower abdominal pain and fever (38.6°C) of 2 months duration. Sovrapubic and transrectal ultrasound (TRUS) (Figure 1) showed a 9 cm solid intravesical mass that occupied the bladder lumen; the ecopattern was characterized by an echoic mass provided of colour signal surrounding a large central hypoechoic area without colour signal in accordance with the presence of necrosis.

At thoracic and abdominal helical computed tomography (CT) (Figure 2) scan the mass was provided of contrast enhancement but no hidronephrosis or distant metastases were found. Bone scintigraphy and digital rectal examination were negative, PSA was equal to 2.9 ng/mL and rou-

Figure 1.

TRUS shows a giant intravesical solid mass.

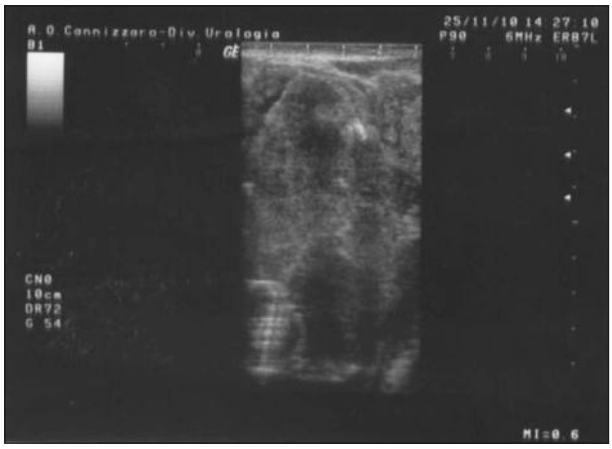


Figure 2.

Abdominal CT scan shows a giant intravesical mass.

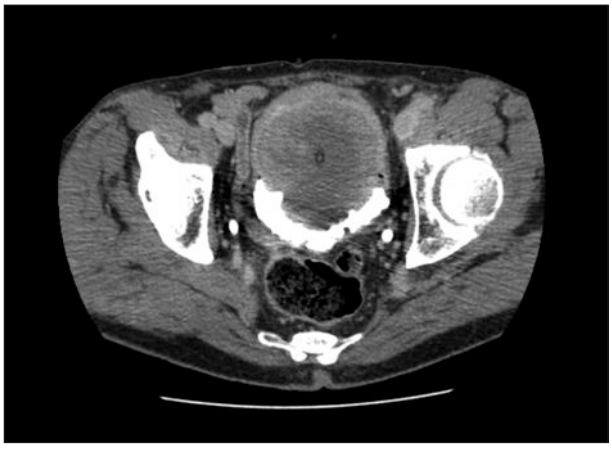
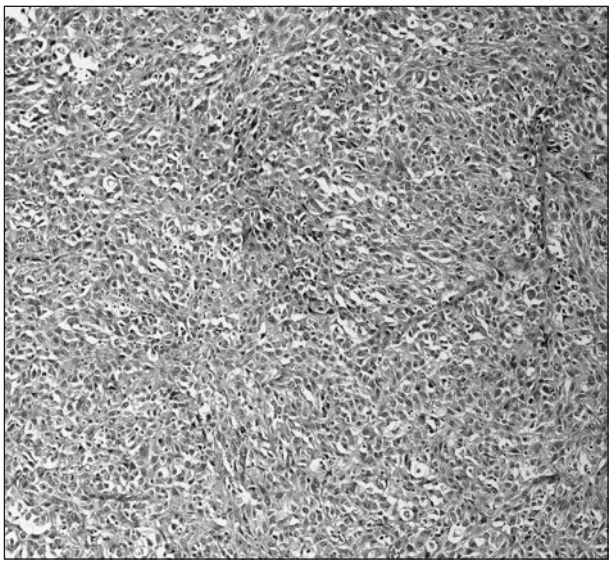


Figure 3.

Tumour was composed of epithelioid and spindle cells. Tumour cells presented large nuclei with evident nucleoli. Mitoses were easily seen.



tine laboratory analysis demonstrated only an abnormal leucocitosis (WBC count of 48.000). At flexible cistoscopy the mass involved all the bladder wall except the trigone reducing the bladder capacity to scarsely 30 ml. Due to this low residual capacity, a TRUS-guided transperineal biopsy of the mass was preferred to a standard bladder TUR; in addition, TRUS guidance allowed to pick-up biopsy samples only from the solid areas provided of colour signal improving the chance of obtaining a sample suitable for histological diagnosis.

TRUS-guided biopsy diagnosed a sarcomatoid carcinoma and a radical cystectomy with pelvic limphadenectomy and cutaneous ureterostomy was performed. Grossly the bladder was occupied by an ulcerated polypoid lesion measuring 9.5 cm in the maximum diameter. The lesion involved the bladder neck as well as the lateral wall of the bladder. Histologically the tumour was mainly composed of anaplastic epithelioid and spindle cells, ulcerating the mucosa and infiltrating the bladder wall (Figure 3).

Mitoses were easily seen as well as foci of necrosis. Foci of urothelial carcinoma in situ was also present in the adjacent urothelium thus supporting the urothelial origin of the lesion. Immunohistochemical study revealed reactivity for epithelial membrane antigen, cytokeratins and vimentin. A final diagnosis of pT3a N0 sarcomatoid carcinoma of the bladder was rendered. Interestingly, the final histology confirmed the biopsy diagnosis.

One month after surgery the patients underwent adjuvant chemotherapy performed in an Oncology department.

Conclusions

SCB is defined by the WHO as a biphasic tumor consisting of admixed malignant epithelial and mesenchymal elements (2). Some Authors argued that these tumors develop as a result of the ability of indifferentiated, neoplastic cells to undergo multiple pathways of terminal differentiation into either mesenchymal or epithelial elements.

Microscopically, SCB is a biphasic tumor made of an intimate admixture of carcinomatous and sarcomatous components with abrupt or gradual transition from one to the other. Clinically, SCBs occur more commonly in older males and present as advanced stage, rapidly growing polypoid lesions sometime mimicking a giant mass (3, 4).

The scarsity of published cases makes it impossible to establish a standardized treatment. In contrast to superficial transitional cell carcinoma, non muscle-invasive SCB usually involves the lamina propria and TURB or partial cystectomy carries the risk of incomplete tumor removal (1).

Therefore, radical cystectomy appears to be the treatment of choice for both superficial and muscle-invasive SCB (5). Although some Authors (6, 7) advocated radical cystectomy plus various combinations of neoadjuvant or adjuvant chemotherapy (ovarian or sarcoma-type chemotherapy regimens) and/or radiotherapy, others (8) reported a poor outcome regardless of the type of treatment. The ultimate prognosis of this tumor remains poor, even in cases of resectable mass.

Wang et al. (1) identified between 1973 and 2004 221 patients with bladder SCB (median age 75 yrs): in 72.5% of them regional or distant metastases were found at diagnosis and the survival rate at 1, 5 and 10 years was equal to 53.9%, 28.4% and 25.8% (median overall survival: 14 months).

Previously, *Lopez-Beltran et al.* (8) reported a mortality rate of 80% at a mean follow up of 14 months with pathologic stage being the most influential prognostic factor.

Wright et al. (6) compared the overall (unadjusted) survival rate for 46,515 patients with urothelial bladder carcinoma, 135 with SCB and 166 with carcinosarcoma showing that it was equal to 77%, 54% and 48% at 1 year, and 47%, 37% and 17% at 5 years, respectively. SCB and carcinosarcoma presented at a similar age decade but at a more advanced clinical stage with more frequent regional and distant metastases when compared to urothelial carcinoma. Moreover, overall mortality was higher with carcinosarcoma than with SCB offering some justification for considering carcinosarcoma and SCB two separate entities.

In conclusion, SCB is a rare and highly malignant neoplasm, occurring predominantly in elder males at an advanced stage, whose prognosis is poor in most cases.

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CASE REPORT

Renal cell carcinoma and synchronous thyroid metastasis with neoplastic thrombosis of the internal jugular vein: Report of a case

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Summary

A case of thyroid metastasis of a renal clear cell carcinoma is presented. The fine-needle aspiration cytology pointed out the primary tumor origin. The patient underwent robot-assisted radical nephrectomy and contextual thyroidectomy. During the operative procedure, a neoplastic thrombus extending from the thyroid metastasis and protruding into the internal jugular vein was found. As a result, thrombectomy and ligation of the internal jugular vein were required. In cases of single synchronous thyroid metastases form RCC, radical surgery should be advisable. Robotic approach allows to associate major surgery procedures, as nephrectomy, with radical metastasectomy.

KEY WORDS: *Renal carcinoma; Synchronous thyroid metastasis; Internal jugular vein thrombosis; Robot assisted nephrectomy.*

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INTRODUCTION

About 25-33% of patients with renal clear cell carcinoma (RCC) presents metastatic foci at the moment of diagnosis, and 40-50% of patients develops metastases after diagnosis (1, 2). Metastases to the thyroid gland are rather uncommon (2-3%) (3), despite its excellent blood supply. On the other hand, thyroid localization of RCC is marginal (1%) compared to the classical metastatic sites (4). Moreover, synchronous presentation is even more rare (only 11 of 150 patients recently reviewed by *Duggal and Horattas* (5)).

Metastases from RCC into the thyroid prevail in clinical series, principally due to a more favorable clinical history of renal carcinoma, with an average time from diagnosis of the primary tumor to metastasis to the thyroid gland, of more than 100 months (6, 7). Pulmonary, melanoma or breast cancer metastases are more frequent reported in autopsy than in clinical series (6, 8-10). The tendency of RCC to the extension by mean of neoplastic thrombi to larger veins in the retroperitoneum is well known. Even in different environments such as the neck, this veinotropic grow pattern seems to be maintained, mimicking the grow pattern of the primary tumor (11, 12).

We present a case of a 83-year-old woman which presented with a thyroid palpable mass and a slight alteration of thyroid function serum values; after fine-needle aspiration cytology (FNAC), the mass resulted to be a RCC metastasis.

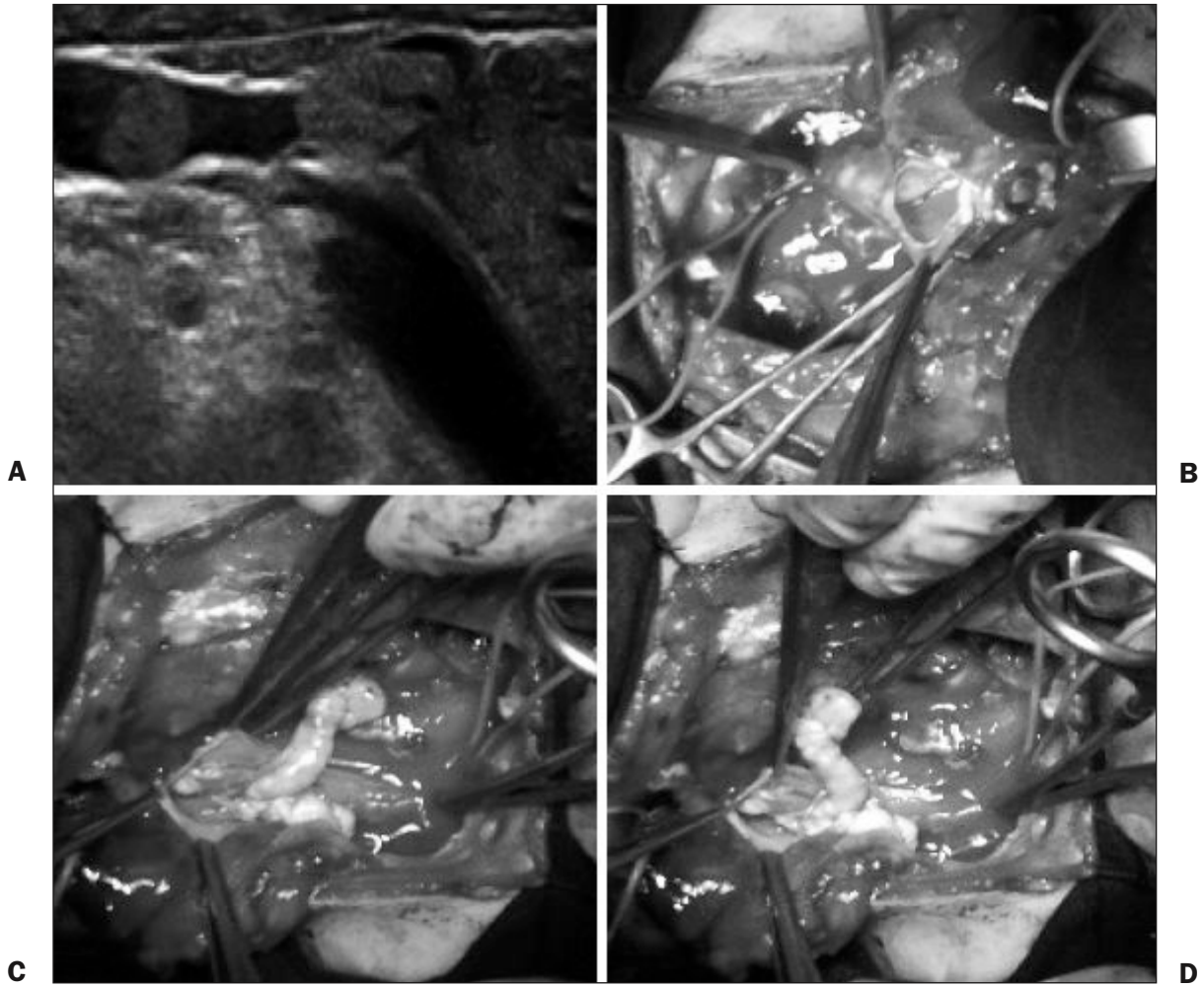
CASE REPORT

A 83-year-old woman (with a history of hypertension, hypercholesterolemia, and stroke with left hemiparesis and aphasia, completely restored) presented a thyroid palpable mass, clinically suspected to be a multinodular thyroid goiter.

Thyroid function serum values were just slightly altered: TSH 0,16 µUI/ml (normal range (n.r.): 0,34-5,60 µUI/ml), fT3: 2,22 pg/ml (n.r. 2,50-3,90 pg/ml), fT4: 1,33 ng/dl

Figure 1.

Neoplastic thrombus into the internal jugular vein: A) intraoperaotory US appearance; B) thrombus visualization after longitudinal venotomy; C, D) intraoperatory appearance of the origin of the neoplastic thrombus.



(n.r. 0,61-1,12 ng/dl). Neck US showed an enlarged thyroid with multiple and merging bilateral hypoechoic nodules. FNAC revealed an RCC localization.
Renal symptoms were absent while serum creatinine was 1,05 mg/dl. The CT scan successively performed showed a large, disomogeneous and partially necrotic mass involving the mid-lower part of the right kidney, without evident renal vein or inferior vena cava thrombosis. No lung or bone lesions were evident.
A minimally invasive approach was proposed for the renal mass in order to simultaneously perform the thyroidectomy. Thus, the patient underwent a robot-assisted nephrectomy (RARN) with a Da Vinci (TM) Standard Surgical System, followed by a total, parathyroid sparing, thyroidectomy. As, during the procedure, thrombosis of internal jugular vein and right superior thyroid vein was found (and confirmed by intraoperatory echoDoppler) (Figure 1A, B, C, D), thrombectomy and ligature of the internal jugular vein were also performed, following the same surgical principles of vein manipulation as in the case of renal vein involvement. The primary tumor turned out to be a Fuhrman grade 2 RCC, with initial invasion of the renal vein and with focal invasion to the perinephric fat. The thyroid was involved by multiple RCC metastases and macro-/microfollicular nodular hyperplasia. The postop course was excellent (no blood supply, nor important analgesic therapy required) and the patient was discharged on day 3 after surgery, with thyroid substitutive therapy. After 14 mos of follow-up, the patient is still in a NED status.

Discussion and review of the literature

As previously mentioned, despite its rich blood supply, the thyroid gland is a rare site of solid tumor metastases: the prevalence of intrathyroid metastases ranges from 1,9% to 25% (13, 14) in autopsy series of patients who die of malignant tumors of other primary sites. The cause of this variability can be found in selection biases and in bad quality of pathological examinations (15).
Moreover, an abnormal thyroid gland (found in about 42% of cases (16), with disrupted blood flow (for ade-

nomas, thyroiditis, malignancies) may affect the incidence of metastatic carcinoma to the thyroid (15). In fact, a nodular hyperplasia was found in our case, too.
The most common carcinomas metastasizing to the thyroid gland are lung, breast, kidney, stomach and melanoma (13). Among them, RCC seems to be a common solid-tumor-source of metastases to the thyroid gland (8), in a percentage of cases varying from 33 (6.) to 76 (17). On autopsy series the incidence of kidney metastases is lower (12%) (18) than that of lung (3), melanoma (39%) or breast cancer (21%) (19).
Leva was the first to describe, in 1891, thyroid metastases from RCC (20). In a review of 113 cases (21), the female to male ratio was 1.35:1 and the primary renal cancer was almost always unilateral (90%) with no significant side preference, whereas bilateralism of thyroid metastases was relatively more frequent (28%).
This condition, found in approximately 1% of patients with RCC (16), has often been considered a terminal phenomenon (6). Anyway clinical significance of thyroid metastases seems to be much lower than the incidence found in autopsy series as they become clinically apparent only in 5% to 10% of patients (18), but it is strongly related with the presence/absence of metastases in other organs (lung 56%, adrenals 19%, liver 13% (12).
Ultrasound is not specific for RCC metastatic thyroid nodules, and scintigraphy often shows a cold nodule in a context of normal thyroid function (16). Generally only FNAC allows the characterization of thyroid masses (22), revealing often also the origin of the tumor (14). However, because of the presence of clear cell component in both RCC and thyroid follicular carcinoma, using FNA cytology alone may lead to a heightened potential for misclassifying metastatic clear cell tumors and incorrectly determining the primary source (23).
RCC shows a well known predilection to spread through larger veins in the retroperitoneum to all venous vessel. This invasive growth pattern seems to be preserved even as concerns the metastases. In fact, in one of the largest series of RCC metastases into the thyroid (16), describe the microscopic pattern as characterized by neoplastic cells infiltrating the capsule with invasion of small to medium vessels. Nevertheless, macroscopic involvement of the internal jugular vein by a neoplastic thrombus extending from a RCC metastasis in the thyroid gland was reported only in other 4 cases (12, 24). The extension to the vein is associated with extrathyroidal tumor growth (43% vs. 0%; p = 0.05) and strongly affects the cause-specific mortality after thyroid operation: the mean OS was 10 months vs. 47 in patients without vein invasion (p = 0.03) (12).
Complete excision of isolated metastasis is associated with a better prognosis (16, 25, 26). In the series of an overall excellent prognosis for RCC patients with solitary metastasis was also found. Furthermore, intrathyroid metastasis from RCC display a better prognosis with a longer survival time (80% at 2 yrs after thyroidectomy) than any other cancer (20% at 2 yrs after thyroidectomy) that metastasizes to the thyroid gland (27). These studies are further highlighting the necessity for surgical resection of solitary metastatic foci to the thyroid gland to assure the possibility of a favorable clinical outcome.
Even if minimal evidence suggests that nephrectomy can induce regression of distant metastases (especially in the lung), a nephrectomy performed with the hope that it will be followed by spontaneous regression of metastases is not advised. However, according to the EAU Guidelines 2009 (28, 29), radical nephrectomy may maintain some indication in selected cases with metastatic RCC as it may prevent severe bleeding, pain and paraneoplastic symptoms.
On the contrary, as previously showed, complete removal of metastatic lesions (especially if metachronous) brings to an improvement of clinical prognosis (30-32).
As a consequence, even in cases of single (or low-number synchronous metastases), if feasible, removal of the primary tumor and of the metastases, at the same time, should be strongly advisable. In these cases, the use of minimally invasive approaches is advisable, too. The development of minimally invasive approaches allows to perform major surgery (as nephrectomy) in patients with advanced stages of disease, without increasing the operatory risks and with an excellent recovery of the quality of life. Following the successful application of the DVSS™ in minimally invasive radical prostatectomy, robotic assistance has been applied to several laparoscopic surgeries of the upper and lower urinary tract, among which radical nephrectomy (33).
Feasibility studies, like the one of *Klingler et al.* (34), show that robotic surgery represents a reproducible technique to perform radical nephrectomy, even if its advantages have to be weighed against its cost (35).
In our case the use of robotics allowed us to perform meanwhile both nephrectomy and surgical radical removal of the thyroid metastasis, strongly minimizing the impact of the surgery on the patient despite the association of two important procedures.

Conclusions

Gross invasion of the internal jugular vein by the neoplastic thrombus of a RCC thyroid metastasis is very rare. Radical surgery may importantly improve survival. Robot assisted (i.e. minimally invasive) approach allowed us to successfully perform radical nephrectomy associated with total thyroidectomy in this case of single synchronous RCC metastasis.

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ORIGINAL PAPER

Transvestibular urethrolysis

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Summary

Objectives: *Bladder outlet obstruction with obstructive and irritative urinary symptoms may be a complication of surgery for female urinary incontinence. In presence of persistent symptoms the therapy is surgical and usually consists in an accurate urethrolysis. The way of approach is generally transvaginal. In this paper we propose and describe our experience with a transvestibular approach.*

Methods: *From 1995 to 2009 18 women who had undergone anti-incontinence surgery (TVT 12 pts, TOT 3 pts, Burch retropubic colposuspension 3 pts) with obstruction and/or irritative symptoms underwent to a transvestibular urethrolysys. Five patients had urinary retention the other patients had post voiding residual urine > 100 ml.*

With a scalpel blade a circum-meatal incision was performed and the urethra was progressively freed, dissecting just below the os pubis upwards and on the vaginal wall downwards untethering it under direct vision obtaining a complete circular freeing of the urethra; at the end the urethral meatus is repositioned with circular stiches.

Results: *The operation lasts between 20 and 40 minutes. Urethral catheter was left in place for 24-48 hours and no complications were observed. The post-voiding residual urine decreased in all the cases and the irritative symptoms were reduced.*

Conclusions: *The transvestibular approach represents a safe and effective approach to urethrolysis undependently of the type of anti-incontinence surgey carried out. Urethrolysis has the advantage of working in a relatively unscarred tissue, can allow a complete untethering of the urethra even in the retropubic space and leaves the vaginal wall intact.*

KEY WORDS: *Female urethra; Bladder outlet obstruction; Urethrolysis.*

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INTRODUCTION

Bladder outlet obstruction is a potential complication of surgery for female urinary incontinence and occurs with an incidence variable from 2 to 22% in the literature (1). It causes symptoms of different intensity either obstructive such as partial or total urinary retention, positional voiding, hesitancy, and/or irritative such as frequency, urgency and urge incontinence (2). A sling procedure is nowadays the most common surgical treatment of female stress urinary incontinence, but obstruction can come to pass also with other type of operations, nowadays more rarely performed, such as retropubic colposuspension (3). After an initial period of observation and medical therapy, in presence of persistent micturition troubles the therapy is surgical and consists in an accurate urethrolysis associated with freeing of the retropubic space or section of the suburethral sling or alternatively with a downward mobilization and loosening of the tape. The way of approach is generally transvaginal and has proven to be effective and affected by a low rate of complications. However this access is not always easy because of the scarred tissue which can be encountered. In this paper we propose and describe a transvestibular approach though a similar operation was already described in 1999 (4), but in the literature it is rarely quoted.

MATERIAL AND METHODS

The charts of 18 women who had undergone various procedures of anti-incontinence surgery from 1995 to 2009 and who presented clear symptoms of obstruction were reviewed.

These patients had undergone preoperative urodynamic

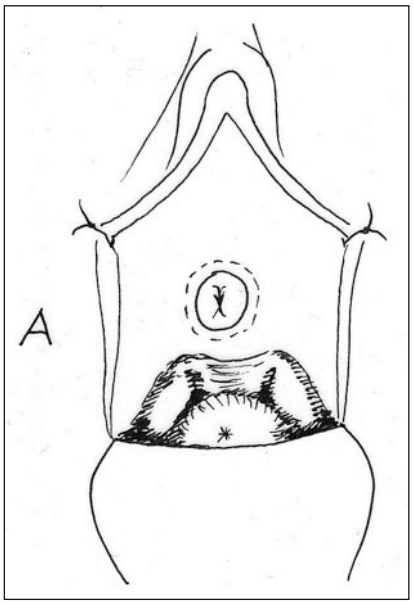


Figure 1a.

Dot line indicates the circum-meatal incision.

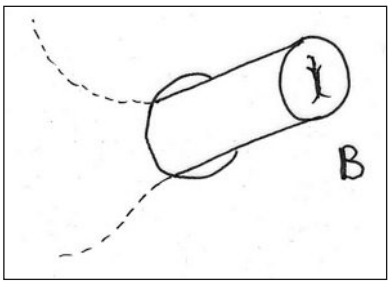
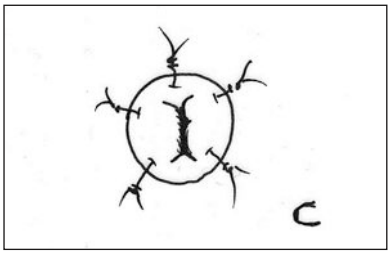


Figure 1b.

Complete isolation and mobilization of the urethra.



Figures 1c.

Reposition and suture of the urethral meatus.

examination and flexible urethrocystoscopy to exclude detrusor instability and/or urethral stricture.

All the patients underwent a transvestibular urethrolysis. The delay from the first operation to urethrolysis varied from 3 to 12 months and all the patients had tried some form of medical therapy with alpha-1 adrenergic blockers or parasympaticolytic drugs in case of severe irritative symptoms. Five patients had an almost complete urinary retention and practised autocatherization since the first operation. The other patients had a more or less important post voiding residual urine > 100 ml, with occasional need of autocatheterizazion. All the patients complained of intense dysuria and many of them were constrained to void in a semi-standing position. The first operation was TVT in 12 cases, TOT in 3 cases and a Burch retropubic colposuspension in the other 3 cases. 12 cases had been operated elsewhere and 6 had undergone operation in our department. (5 TVT and 1 TOT).

The urethrolysis was performed in most of the cases under general anaesthesia with the patient in moderated dorsal lithotomy position. In few patients an epidural anaesthesia was utilized. In all the cases the choice of the type of anaesthesia was left to the anaesthesiologist. The surgical field was prepared and draped and a 16 F Foley catheter was inserted into the bladder. With a scalpel blade n. 11 a circum-meatal incision was performed (Figure 1a) and with subtle tip scissors a periurethral dissection was started. The urethra was progressively freed, dissecting just below the os pubis upwards and on the vaginal wall downwards. On either side it is generally not necessary to enter the pelvic space, perforating the urethropelvic ligaments, but, if needed, it can be done without any problem. In case of previous sling procedure, the suburethral tape can be rapidly found, freed and sectioned or mobilized. In all the cases we have sectioned the tape just in its mid-line. In the patients undergone to a retropubic procedure the urethra is extensively mobilized anteriorly from the undersurface of the pubis, untethering it under direct vision and approaching the retropubic space to remove sutures and/or adhesions, thus obtaining a complete circular freeing of the urethra, which is telescoped into the surgical field (Figure 1b). At the end of the dissection, the urethra is repositioned and few circular stiches recreate the original position of the urethral meatus (Figure 1c).

Results

The operation lasts between 20 and 40 minutes. No complications were observed. The urethral catheter was left in place for 24-48 hours and after its removal all the patients resumed spontaneous micturition.

The post-voiding residual urine decreased in all the cases and remained below 50 ml and no more catheterisms were necessary in any patient. The irritative symptoms were generally lessened, although in few patients persisted to some extent for long time, but could be tolerated rather well, with the aid in some patients of parasympaticolytic drugs. In no case there an urinary infection was observed.

Discussion

Bladder outlet obstruction with obstructive and irritative urinary symptoms is a well known, even if not frequent complication of antincontinence surgery. In severe cases medical therapy is generally ineffective and patients, other than being bothered by troublesome irritative symptoms, as frequency and urgency, must often recur to authocatheterization, routinely or occasionally, and complain of dysuria with obliged semi-standing positional voiding. In these cases an urethrolysis is indicated with section of the suburethral tape when present. This type of treatment is generally effective, even if in many cases a de novo stress urinary incontinence may occur, which needs an iterative anti-incontinence surgery. The urethrolysis, which foresees the freeing of the urethra from its adhesions to the surrounding tissues and the section of the sutures or of the prosthetic tape is a procedure not alwys simple, because of the postoperative scarred tissue which

makes dissection sometimes difficult, exposing the urethra to potential injuries. The retropubic approach described by Webster and Kreder (5) is a major operation and is no more performed.
The most frequently adopted approach is transvaginal and good results and few complications are reported with this operation (5-7).
However, the identification of the correct plane of dissection between the anterior vaginal wall and the urethra with its tape is not always comfortable because of the scarred tissues we can encounter and the final repair of the surgical incision implies a vaginal line of suture, which, in case of urethral injury, can entail the risk of a urethro-vaginal fistula. Besides, a future anti-incontinence surgery by an iterative transvaginal approach can offer additional difficulties (8).
The transvestibular approach, which, to the best of our knowledge, is little known in the literature, represents an elegant, safe and effective approach to urethrolysis, independently of the type of anti-incontinence surgery carried out during the first operation. It is simple, has the advantage of working in a relatively unscarred tissue, can allow a complete untethering of the urethra even in the retropubic space and leaves the vaginal wall intact.
The urethra can be completely freed under direct vision, making the possibility of urethral injury uncommon. Besides, in case of injury, the repair is much safer, because the untouched vaginal wall is an effective barrier against the fear of developing an urethrovaginal fistula.
The suburethral tape, when present, can be quickly found and sectioned. At the end of the procedure the urethra is repositioned orthotopically, making the development of a de-novo incontinence less frequent than in other type of operations. The interposition of a Martius flap as suburethral support is possible (10).
In the cases in which we had to reinsert a second tape for a de-novo severe incontinence we did not experience any difficulty nor complication, intraoperatively or postoperatively.

Conclusion

The transvestibular approach to urethrolysis is a simple and effective way of approach which deserves to be more known among urologists and gynecologists.

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CASE REPORT

Blue nevus of the prostate: Incidental finding in radical prostatectomy specimen with a pre-operative echographic image of peripheral hypoechogenic nodule

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Summary

Blue nevus is a stromal melanin deposition, which is microscopically characterized by deeply pigmented melanin-filled spindle cells within the fibromuscular stroma. Cases with prominent melanosis such as those with grossly visible pigment are uncommon. Melanocytic lesions of the prostate are incidental findings with no evidence of malignant transformation. There have only been very few reports of a malignant melanoma of primary prostatic origin. We report an incidental finding of a blue nevus of the prostate, in a radical prostatectomy specimen, in a 64-years-old man with a pre-operative ecographic image of peripheral hypoechogenic nodule. The are very few reports of blue nevi associated to prostatic adenocarcinoma, but none has been evidentiated before surgery as a distinct ultrasound lesion interpreted as adenocarcinoma, therefore inducing the clinician to perform biopsies and consequently a radical prostatectomy.

KEY WORDS: *Blue nevus; Prostate; Peripheral hypoechogenic nodule; Adenocarcinoma.*

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INTRODUCTION

The identification of melanocytes within the fibromuscular stroma and/or within epithelial cells is uncommon in the evaluation of prostate specimens. Nevertheless, it has been proved that melanoblasts arise from the neural crest and migrate from the neural crest to all parts of the body (1).
Melanotic lesions of the prostate consist of cases with stromal melanin alone, or glandular melanin, or both. The term "*melanosis*" usually refers to melanin found in any localization within the prostate. Blue nevus identifies a stromal melanin deposition, while, the term "*glandular melanosis*" denotes the presence of melanin within epithelial cells.
Microscopically, blue nevi are characterized by deeply pigmented melanin-filled spindle cells within the fibromuscular stroma. The incidence of microscopic focal prostatic blue nevi or glandular melanosis is about 4%. Cases with more prominent melanosis such as those with grossly visible pigment are much less common, and they are reported as isolated case reports (2-4).
Melanocytic lesions of the prostate are incidental findings with no evidence of malignant transformation. There have only been very few reports of a malignant melanoma of primary prostatic origin. Nevertheless, most cases attributed to the prostate actually originate from the prostatic urethra (5).
Herewith, we report an incidental finding of a blue nevus of the prostate, in radical prostatectomy specimen, in a 64-years-old man with a pre-operative ecographic image of peripheral hypoechogene nodule.

CASE REPORT

Clinical findings

A 64-years-old man was admitted to the urology department for a check-up subsequent to a PSA serum elevation. Physical examination showed a diffusely enlarged prostate gland of rubbery consistency. He underwent therapy with

alpha-litic and dutasteride, but after six months there were no variations in serum marker levels and/or prostate size. An ultrasound scan showed prostate with a mean diameter of 5.5 cm with the presence of bi-lobated adenoma of 6.0 cm transverse diameter with calcifications in the prostate pseudocapsule, showing also the presence in the left para-median site of an hypoechogenic nodule of 1.0 cm (Figure 1A). Prostatic biopsy showed the presence of few isolate glands of adenocarcinoma in a context of a benign prostatic hyperplasia. Consequently, patient underwent radical prostatectomy with removal of seminal vesicles and iliac-obturator lymph-nodes.

Tissue specimens, pathology and Immunohistochemistry

Grossly, prostate measures were 6.5 x 5.0 x 6.5 cm. The section of the specimen showed a black nodule in the left lobe which was well defined compared to the adjacent tissue. Some black stria diffused in the prostatic tissue were also observed (Figure 1B).

Specimen was fixed in 10% buffed formalin, embedded in paraffin, sectioned, and stained with hematoxylin-eosin. Immunohistochemical stains were performed with the following markers: HMB-45, MART-1, S100, CD68, and Ki67. Appropriate positive and negative controls were included. Histological examination of the specimen showed hyperplasia of the glandular and stromal elements and a large pigmented area was encountered on the histologic sections of the left side of the gland, in the paramedian peripheral site. Pigmentation of the prostate occurred with a dense cluster, with a sort of peripherical pigmentate scattered feature. The fibromuscolar stroma was characterized by a proliferation of elongated, bipolar, spindle-shaped cells, sometimes grouped in short fascicles. The melanocytes showed elongated dendritic processes and contain variable amounts of melanin pigment in the cytoplasm, including within the dendritic processes; there were also scattered melanophages (Figure 2A and 2B). The cytoplasms of melanocytes presented HMB-45, MART-1 (Figure 2C and 2D), and S100 positive staining, while were negative to CD68. The melanocytes showed a low proliferative index as indicated by Ki67.

In addition, a careful examination of all prostatic tissue showed the presence of few isolated foci of acinar adenocarcinoma limited to less than a half of the right lobe. Lymph-nodes were negative. The Gleason score was 3+3. By comparison with echographic data, we identified the area of prostatic tissue rich of melanocytes as the hypoechogenic nodule which was suspected by ultrasound to be adenocarcinoma of the prostate.

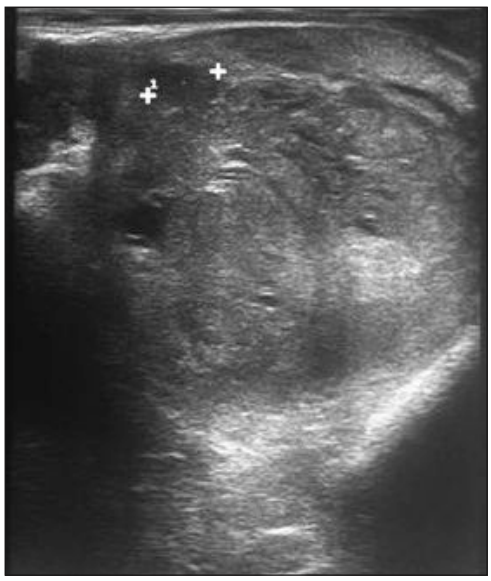
Discussion

Description of blue nevi as incidental microscopic findings is reported in cases of prostate removed for benign fibromuscolar and adenomatoid hyperplasia. Blue nevus was first reported in the prostate by Nigogosyan et al. in 1963 (6).

Isolated melanoblasts and benign melanocytic lesions have been described in a variety of mucosal and visceral sites. In the literature, it is speculated whether these are precursors of melanomas. However, malignant transformation of blue nevus in the prostate is highly unlike, since malignant change has rarely been reported only in the cellular variant of blue nevus of the skin (7, 8).

Recognition of this entity is important to the clinician because the lesion in the prostate grossly can simulate a malignant tumor of the gland.

In this case, the pre-operative check up showed ultrasound findings highly suspicious for adenocarcinoma of the gland, and random biopsy showed the presence of adenocarcinoma in few isolated glands. The finding of isolated gland of adenocarcinoma was confirmed by the subsequent histologic evaluation of the prostate specimen, but the image of a tumor nodule in the paramedian left lobe was found to be a blue nevus without any malignant feature. The immunohistochemical analysis confirmed the melanocytic nature of the lesion in the paramedian left lobe. In addition, the features as the absence of tumoral necrosis, cytologic atypia, and absence of pleomorphism, associated with a low mitotic index and a low proliferative index, ruled out the pres-



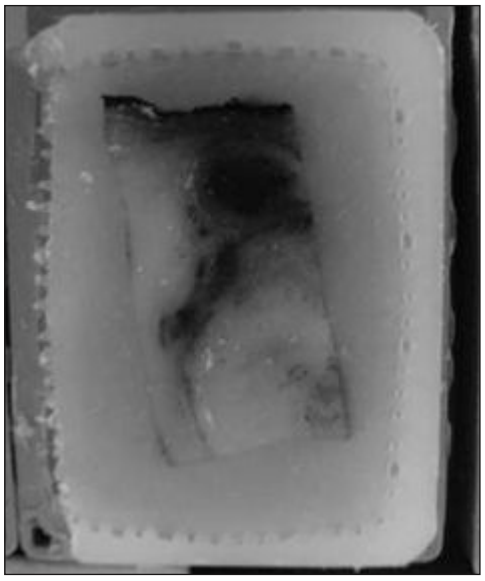
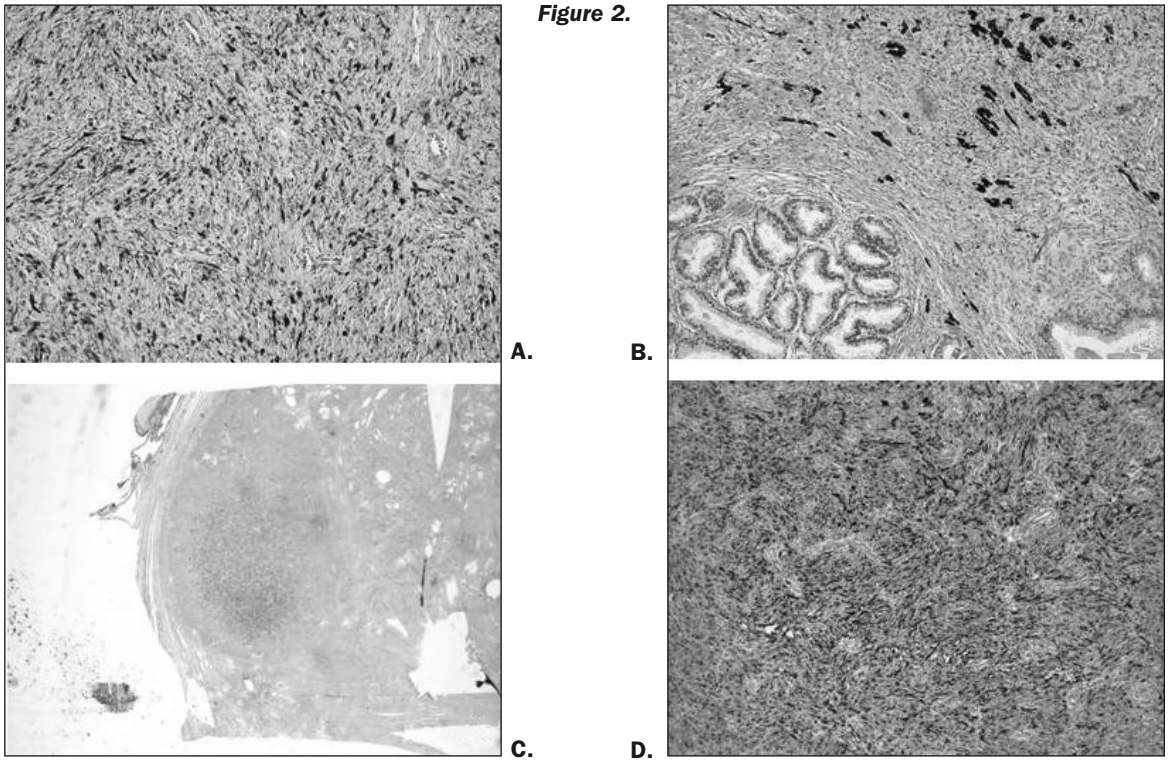


Figure 1.

A. *Ultrasound scan showed the presence in the left para-median site of an hypoechogenic nodule.*

B. *Tissue block showing a black nodule well defined in respect to the adjacent tissue and a black stria in the prostatic tissue.*

Figure 2.



A. *Melanocytes with elongated dendritic processes, some containing cytoplasmic melanin pigment and scattered melanophages (haematoxylin & eosin staining, original magnification x 40).*
B. *Melanocytic cells in prostatic stroma between benign hyperplastic glands (haematoxylin & eosin staining, original magnification x 40).*
C. *HMB45 positive reaction in the blue nevus cells (reaction with red chromogen, original magnification x 1).*
A. *MART-1 positive staining in the blue nevus cells (reaction with red chromogen, original magnification x 40).*

ence of a malignant melanoma and led us to diagnosis of blue nevi of the prostate. The are very few reports in the literature of blue nevi associated to prostatic adenocarcinoma (9, 10), but none as been evidentiated before surgery as a distinct ultrasound lesion interpreted as adenocarcinoma inducing the clinician to perform biopsies and consequently radical prostatectomy.

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REVIEW

Urinary incontinence in adults: Nurses' beliefs, education and role in continence promotion. A narrative review

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Summary

Introduction: *Urinary incontinence (UI) has a high prevalence worldwide, in both genders; the available data suggest that the number of incontinent people will dramatically increase in the next few years. The costs generated by UI are similar to those induced by HIV and breast cancer. We aimed to investigate nurses' beliefs, knowledge and educational situation in the field of urinary continence.*

Methods: *We performed a narrative review of literature, by searching qualitative and qualitative studies (2006-11) in PubMed, CINAHL and the Cochrane Library. Papers investigating pharmacological and/or surgical intervention were excluded. Only studies referred to adults have been taken into consideration.*

Results: *Prevalence ranges from 25 to 45% in women; in men, post-prostatectomy UI occurs in a median of 10-15% of the total cases. Benign prostatic hyperplasia, which affects 50% of men aged 50 to 60, is often associated with urge incontinence. The yearly individual expense for pads in Italy has been estimated to be as high as € 913 in 2004. People often do not know about the possible solutions to UI; nurses seem to lack education in continence promotion, notwithstanding the proven effectiveness of the conservative interventions they could perform in autonomy. In Italy, few academic programs offer nursing education in this field.*

Conclusions: *Urinary incontinence seems to be an underestimated problem; nurses often lack proper education in continence promotion. Academic, structured courses would be a solution; however, since education itself is not sufficient to really improve clinical practice, organizational support would be required to effectively promote continence in the broadest possible population. This would be a long-term investment for both quality of care and costs. Further studies are needed, regarding conservative management of UI; research could lead to a strong integration between clinical and academic branches of nursing, resulting in good quality evidence for clinical practice.*

KEY WORDS: *Urinary incontinence; Adult; Health promotion; Nursing education.*

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INTRODUCTION

The *International Continence Society* has defined urinary incontinence (UI) as "*any involuntary loss of urine*" (1). The number of people with UI has been increasing over the years, due to the trends of prostatic cancer requiring radical surgery, aging of population and the increasing number of diseases which may interfere with continence (e.g. diabetes and neurodegenerative diseases), with considerable impact on both quality of life and costs. Therefore, it is necessary to apply every possible strategy to prevent and conservatively manage this problem; this paper discusses the social and economic relevance of UI, as well as nurses' knowledge, beliefs and educational situation, and proposes possible solutions for this issue.

METHODS

We searched PubMed, CINAHL and The Cochrane Library for both primary and secondary literature, regarding adults and published in English, Italian, Spanish and French from 2006 to 2011, even if an older

study had to be included (2) due to the lack of more recent evidence. We were unable to find in literature the exact name and citation of an important study, carried out by the *International Continence Society* in 2003 (see paragraph "*Nurses' role in promoting continence*"), so we cited the book that contained it (3). We considered both qualitative and quantitative studies, and excluded papers presenting pharmacological and/or surgical interventions. As regards epidemiology, we only searched for secondary literature, given the considerable differences (methodology, definitions, and assessment times) between the available studies. We took into consideration 7 reviews and 16 single studies; Table 1 shows our strings and their results.

Results

Epidemiological and economic relevance of UI

Prevalence data show considerable variability, due to differences among the surveyed populations and the methods used; a recent paper from the International Consultation on Incontinence reports prevalence data of 25 to 45% in women (4). In this gender, the median level of prevalence estimates shows a positive trend in UI during adult life (20-30% from 20 to 39 years, 30-40% from 40 to 59 years, 30-45% over 60). As regards severe incontinence, most studies report data ranging from 6 to 10%. The number of deliveries, accounts for incontinence (5); in particular, a systematic review reports that 31% of women have UI in the first three months after vaginal delivery (6). High prevalence data do not lead to equivalent rates of consultations with health care professionals, since only 15% of women with UI in the USA seek advices from a clinician (7). This fact could be related to social taboos, which foster social embarrassment and prevent patients from seeking solutions different from pads (e.g. conservative management). Fewer studies are available in male populations; literature findings show a median prevalence of 10-15% for post-prostatectomy UI (range: 2-57%) (3). Stress incontinence seems to be the most frequent, especially among men who underwent radical prostatectomy (8). Urge incontinence is associated to benign prostatic hyperplasia, a condition found in approximately 50% of men aged 50 to 60 years and up to 90% in people over 80 (9).

In both genders, UI is influenced by age and BMI (10), as well as by neurodegenerative diseases (e.g. Parkinson's) and diabetes (11), while caffeine seems to play a marginal role as a risk factor (11).

In 2006, a literature review carried out by the European Association of Urology (EAU) in both male and females with overactive bladder (OAB), reported 20.2 million symptomatic people over the age of 40 in Italy, German, Spain, Sweden, and the United Kingdom (12).

According to the statistical model proposed by the authors, this number is expected to rise to 25.5 million by 2020, with 9 million patients affected by urge incontinence. In nursing homes, where the mean age of patients is higher, the prevalence of UI ranges currently from 31% to 70%, according to secondary literature (13).

UI is the most expensive urological condition, with an economic burden worldwide similar to those derived from HIV/AIDS, asthma and breast cancer (3). The EAU paper showed an individual yearly expense of €761 for drugs in Italy; it also pointed out that the diagnoses-related group (DRG) reimbursement for fall and fracture, which could recognize UI as a risk factor, had a tariff of €3894 for each patient. The same paper reported that pads were used by 63% of the Italian patients with OAB, causing an individual yearly expense of €913 (12). Moreover, a recent paper reported an increase of 27% in pad costs all over Europe, between 2007 and 2010 (14), so that older data are probably underestimated.

Knowledge and attitudes towards incontinence among nurses

People often do not know that UI, OAB and pelvic organs prolapse can often be treated with success; as regards nurses' knowledge, evidences are conflicting. A recent study on 1000 nurses (15) pointed out that over one third of the responders had not received any education about caring for incontinent patients during their training; 53% had had no training in this field after registration.

In a cross-sectional study performed on a sample of 199 nurses in a nursing home (16) some authors defined the level of knowledge shown by nurses as "*satisfactory*", based on the number of correct answers given to the questions of a validated questionnaire. However, nurses performed continence-related actions only "*sometimes*" or "*often*" at best, and obtained best results in the fields regarding the support provided to patients. The worst results were found in the "*documentation*" section of the questionnaire. Unfortunately, the study does not provide any information regarding the educational curriculum of these professionals.

According to some authors, teamwork is fundamental for nurses to effectively apply their skills to patients: in the study by *Hagglund* (17) nurses perceived a lack of authority to start nurse-led continence clinics, due to an organization that did not enable

Database	String	Retained articles
PubMed	"Urinary Incontinence/epidemiology" [Mesh] Promotion of urinary continence "Urinary Incontinence/economics" [Mesh] "Urinary Incontinence/nursing" [Mesh]	(1-2; 5; 7-11) (12-14) (6; 11; 15-17) (4; 17-21)
CINAHL	"Urinary incontinence" AND epidemiology Promotion of urinary continence "Urinary incontinence" AND costs "Urinary incontinence" AND nursing	No further articles were found.
The Cochrane Library	Urinary incontinence	(22-24)

Table 1.
Summary of the article search.

nurse-led appointments and the lack of collaborative work in the professional team.
A qualitative study (18) claims that hospital nurses do not routinely perform patients' assessment, and continue to contain incontinence, rather than treat it. Lack of education seems, once more, an important issue.

Nurses' role in promoting continence: educational and research priorities

In literature, few studies are available regarding the suggested characteristics of academic nursing education in the field of urinary incontinence; therefore, the available evidence is based mainly on opinions expressed by experts (grade "D"). For example, *Abrams and Cardozo* claim there is a need for educational programs on incontinence, and suggest mandatory lessons on this topic in the academic education of physicians, nurses, physiotherapists, and other health care personnel. They also suggest considering incontinence as a specific subject, instead of a minor topic; the programs, in their opinion, should be approved by a qualified central institution; as regards nursing, specialized continence nurses would be the best teachers (3). However, education itself is not sufficient to produce a deep impact on clinical practices: the study performed by *Rigby* (2) has pointed out that increased knowledge in the field of UI does not necessarily imply an improvement in clinical nursing. According to the experts, these conclusions also apply to physicians and other professionals (3). Several educational courses exist, in which nurses can learn the theoretical and practical principles of continence promotion; however, many of them are limited in time and placed outside the academic pathways (e.g. programs of continuous education in medicine, seminars, and so on), with exceptions in very few Italian universities.
Abrams and Cardozo point out the need for research, aimed at finding effective ways of instruction for the general public, as well as evaluating the actual impact of educational campaigns for consumers. This last suggestion is supported by the results of a survey carried out in 2003 by the *International Continence Society* (3) and involving continence organizations worldwide. Most associations defined the level of comprehension of incontinence expressed by the general public as "*low*". Eight of them said that "*being uncomfortable with that subject*" was the main reason for mass-media to avoid incontinence; other reported reasons included lack of specific education, shame, lack of interest and the fact that incontinence is not an important matter. As a consequence, people are often misinformed and tend to avoid clinical consultations, maybe considering UI as an unavoidable burden of aging, prostatic surgery or delivery.
According to some authors, nursing interventions seem effective in preventing and treating UI. *Ganz et al.* (19) provide evidence of an improvement in the quality of care for incontinent patients with dementia, when comanaged by nurse practitioners, even in a practice of geriatricians. In a recent Italian study (20), advices from continence nurses, the introduction of new pads and a structured skin care regimen have proven useful in reducing incontinence-associated dermatitis, absorbent product use, and generation of waste materials. The introduction of advices after the other two interventions, produced a statistically significant difference in the outcomes achieved, if compared to those obtained with pads and skin care alone.
It must be pointed out that many of the first-line treatments recommended by the international guidelines can be performed autonomously by nurses. For example, pelvic floor muscle exercises are recommended by the EUA guidelines as grade "A" treatments for UI, both in women and in men. As regards other conservative treatments, such as functional electrostimulation (with or without biofeedback) and extracorporeal magnetic innervation (ExMI), and bladder training , notwithstanding the amount of studies published on this subject (21-24), more evidence is required to clarify the role of exercises over time, as well as the efficacy and safety of ExMI.

Conclusions

Urinary incontinence seems to be an underestimated problem, notwithstanding the huge number of patients it affects, the costs and the deep impact on quality of life. Nurses are often unaware of its importance, and the teamwork delivered by the various health care professionals is sometimes inadequate to fulfill the needs of patients (timely diagnose, effective treatment, correct documentation).
Over the years, many studies have been carried out, regarding frontline treatments such as bladder training, pelvic floor exercises, functional electrical stimulation, and biofeedback; however, all major literature reviews (e.g. Cochrane) have found significant lack of evidence in some aspects of these intervention. Moreover, some therapies like extracorporeal innervation need strong effectiveness evidence. Nurses working in settings that favor rehabilitation, e.g. urologic outpatients, should consider doing research in this field. That could also be a good chance of collaboration between the academic and clinic branches of nursing, given the current availability of academic education in nursing research in Italy (e.g. doctoral programs and post-bachelor courses).
A strong need for nursing education emerges from both literature papers (although limited in number) and the opinion of experts worldwide; we believe that a structured academic path would be the best choice. Nurses who already have a formal education in continence could teach the principles and practice of rehabilitation, and the integration with the academic branch of the profession would provide the necessary research skills. Some experiences like this exist in Italy, but we believe they should become a standard, considering the growing number of incontinent patients, the economic burden for health care organizations, and the need for professional care in many different settings (hospital wards, outpatients, home care, and nursing homes).
Education itself is not sufficient to really improve clinical practice; organizations should support nurses that enroll in continence courses, since having personnel with advanced competences would be a cost-saving investment in the long run. Actually, given the costs of pads and the complications due to UI, maximizing the chances of rehabilitation for the broadest possible popu-

lation would result in saving money, which could be used to further improve the quality of health care services. Moreover, advanced practice nurses could manage several rehabilitation methods autonomously, integrating their activities with those carried out by other professionals when necessary (physicians, physiotherapists, and midwives). This scenario already exists in some Italian hospitals, and could be extended to other types of health care facilities (e.g. nursing homes), providing effective answers to a problem of growing importance.

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Possono far parte dell'Associazione con la qualifica di Socio Ordinario gli Specialisti in Urologia e gli specializzandi in Urologia operanti in strutture assistenziali urologiche dell'Ospedalità a gestione Privata; con la qualifica di Socio Corrispondente gli studiosi italiani o stranieri che abbiano dimostrato un particolare interesse per l'Urologia.

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Iscriversi è semplice, basta scaricare la scheda di adesione presente sul sito **www.urop.it**, compilarla in tutte le sue parti prendendo visione dell'informativa sulla privacy ed inviarla via fax al numero 089 771330, allegando la fotocopia di un valido documento di riconoscimento.

QUOTA SOCIALE

La quota sociale per l'anno 2011 è stabilita in € 100,00 per i Soci Ordinari ed € 50,00 per i Soci Corrispondenti.

Dà diritto alla ricezione della rivista "Archivio Italiano di Urologia e di Andrologia", organo ufficiale della Associazione.
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Per richiedere informazioni contattare il tesoriere
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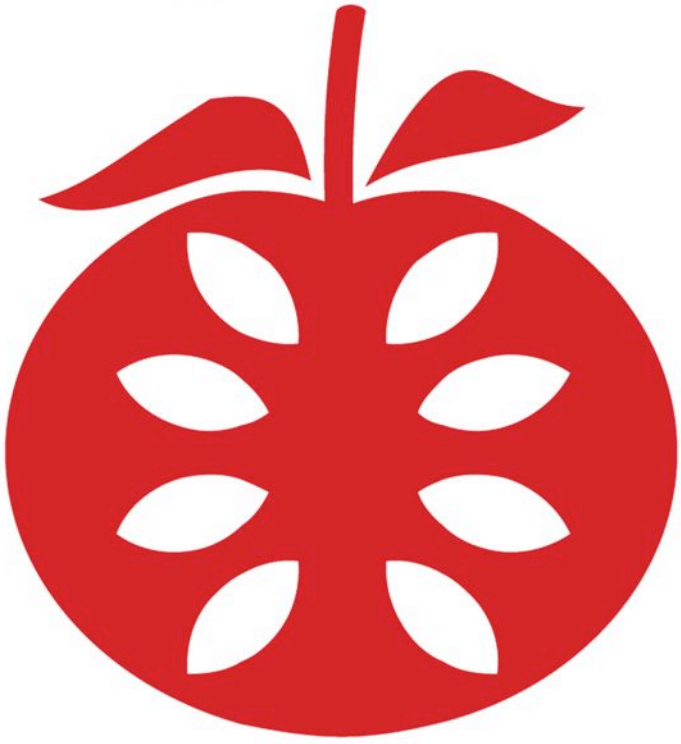

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