Original Article

Endoscopic Enucleation of the Prostate – A Retrospective Single-center Study: Early Outcomes

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Abstract

Purpose: This clinical study was designed to present our initial experience of holmium laser enucleation of the prostate (HoLEP) with the use of the Quanta Litho Cyber Ho 150 W™ (Quanta System, Samarate, Italy). **Materials and Methods:** The data of the current study including all the patients who underwent HoLEP from April 2022 to December 2022 were retrospectively collected. All the operations were performed by the same experienced surgeon and the surgical technique was similar in all the cases. The successful completion of the operations, the operative time, and the major complications were the primary endpoints of this study. **Results:** Fifteen patients underwent HoLEP from April 2022 to December 2022 in our department. The completion of all the surgeries was successful. The average enucleation time was calculated to be 47.13 (±8.44) min, while the morcellation phase was completed in a mean time of 29.8 (±5.35) min. No major complications were noticed. The average hemoglobin drop was 1.4 (±0.69) g/dL. **Conclusion:** Our initial experience and early outcomes of the use of Quanta Litho Cyber Ho 150 W™ (Quanta System, Samarate, Italy) in HoLEP were presented. All the cases were completed successfully, without major complications or significant blood loss.

Keywords: *Benign prostatic hyperplasia, enucleation, holmium laser enucleation of the prostate, holmium, prostate*

Introduction

Benign prostatic hyperplasia (BPH) and the related symptoms constitute an important health-care burden around the world, presenting a prevalence of 50% for men in the 50th decade of their life and rising the annual treatment cost to $776 million in the United States.[1] The transurethral resection of the prostate (TURP) was considered to be the method of choice for the treatment of BPH. Nevertheless, TURP is related to significant complication rates, especially when used for the treatment of large-volume prostates.[2] The introduction of lasers in the armamentarium of BPH contributed to the rapid development of enucleation techniques. The superiority of endoscopic enucleation of the prostate (EEP) with lasers (Holmium or Thulium) or bipolar electrocautery is associated with the theoretical advantage of the capability to excise a greater percentage of adenomatous tissue and to minimize the risk of the BPH recurrence.[3] Endoscopic EEP is associated with lower blood loss and shorter hospitalization time in comparison to open adenomectomy.[4] On the other hand, the endoscopic enucleation techniques are characterized by their steep learning curve, which ranges from 40 to 60 cases according to the current literature.[5,6] In addition, this surgical approach is related to a high rate of stress urinary incontinence (4.9%–12.5%) in comparison to TURP (2%) and open surgery (3%–9%).[7] EEP is an efficient and developing technique for the treatment of BPH, although it should be adopted with safety and guidance.[8,9] The aim of the current study is to present our initial experience and early outcomes of Holmium Laser Enucleation of the Prostate (HoLEP) with the use of the Quanta Litho Cyber Ho 150 W™ (Quanta System, Samarate, Italy).

Materials and Methods

The current study is a retrospective study conducted at the Urology Department of the University Hospital of Patras. The institutional ethics committee approved the study, and informed consent was obtained from all the patients.

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Data collection

The data collected preoperatively included the patient's age, body mass index (BMI), and comorbidities. The prostate volume and the functional parameters of Q_{max} (the highest flow rate measured) and International Prostate Symptom Score (IPSS) were recorded before the procedures and during the follow-up. The operative times, perioperative hemoglobin levels, transfusions rate, intraoperative complications, hospitalization time, and postoperative complications were also recorded.

Study design

Patients who underwent HoLEP using the Quanta Litho Cyber Ho 150 W™ (Quanta System, Samarate, Italy) from April 2022 to December 2022 were included in this study. The procedures were conducted by one expert surgeon with previous specialization and preexisting experience regarding prostate enucleation techniques. As exclusion criteria were considered the prostate volume under 80 cm^3 and over 150 cm^3, serious coagulation disorders or elevated prostate-specific antigen (PSA) according to the age standards. In addition, patients that could not comply with the necessary follow-up were excluded. In case of abnormal PSA level, the patients were evaluated for the possibility of prostate cancer and were excluded from the current study. The final work-up of the patients took place in the Urology Department of Patras with abdominal ultrasonic measurement of the prostate volume, Q_{max}, IPSS, and further urodynamic evaluation when needed. The majority of the patients were initially examined in the outpatient unit, while some of the patients were referred to our department by smaller hospital units.

Surgical technique

Our surgical approach is based on the *en bloc* technique that was described by Saitta *et al*.[10] The patient, under general anesthesia, was placed in the lithotomy position. The resectoscope (Karl Storz SE and Co. KG, Tuttlingen, Germany) was inserted in the urethral lumen for the careful observation of the sphincter and the anatomy of the prostatic urethra. A cystoscopy was conducted for the observation of the orifices and any additional pathological findings. The limit of the external sphincter was marked with an incision between 11th and 1st h using a 550 μm laser fiber. The settings preferred were 100 W for enucleation and 40 for hemostasis with slight differentiations in some cases. To demarcate the sphincter from the apex the same incision was conducted parallel to the verumontanum and afterward the anterior and the posterior incisions were joined. The gentle dissection without excess mechanical stress in combination with the early release of the prostate is believed to contribute to the decrease of postoperative incontinence rate. The incisions were gradually deepened until the capsular tissue was observed, followed by dissection starting with direction from 6th to 12th h and following the enucleation plane circumferentially [Figure 1]. The anterior plane of enucleation was preferred for the entry to the bladder, and the circumferential dissection of the adenoma attached to the capsule inside the bladder neck was dissected with caution, after the careful re-observation of the ureteral orifices. When the adenoma was free, it was pushed inside the bladder. After careful hemostasis, the resectoscope was replaced by a 26 Fr nephroscope (Karl Storz SE and Co. KG, Tuttlingen, Germany). The inflow and outflow channels of the nephroscope were both used for irrigation purposes. The increase of irrigation fluid inside the bladder was important, as it prevented the bladder from collapsing during the morcellation phase. The working channel of the nephroscope was used to facilitate the morcellator (Quanta Blade, Quanta System, Samarate, Italy). After the completion of the morcellation phase, a 22 Fr 3-way catheter was placed with mild bladder irrigation. Trial without catheter (TWOC) was usually performed on the 1st postoperative day and laboratory examinations including hemoglobin were performed the morning before discharge.

Follow-up

The patients' follow-up was realized 1 and 3 months after the procedure at the outpatient unit. Stress urinary incontinence, which was assessed by the need to use any pads, IPSS, and Q_{max} were evaluated.

Endpoints

The primary endpoints of the current study were the uneventful completion of the procedures, the operation time (including the enucleation and morcellation time), the percentage of adenoma removed, and the major complications. Enucleation time was defined as the time between the first and the last activation of the laser device, while morcellation time was the time between the initial and the final activation of the morcellator device. The decrease of hemoglobin as a secondary endpoint was also evaluated preoperatively and postoperatively. The hemoglobin

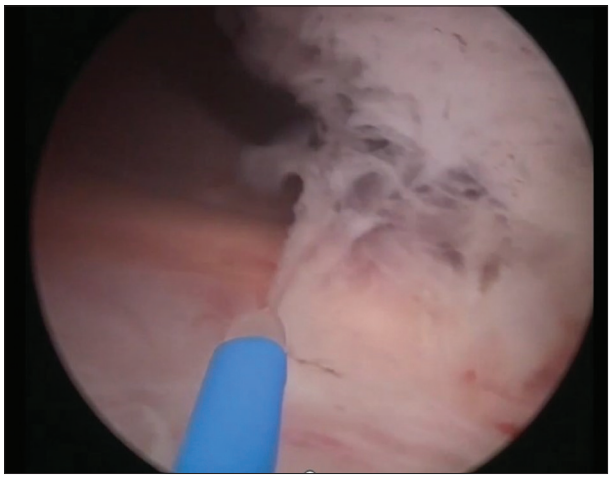

Figure 1: Endoscopic image before the final detachement of the adenoma inside the bladder neck

drop was calculated with the comparison between the preoperative levels and the levels before discharge.

Statistics

The continuous variables were described as mean ± standard deviation. The Categorical variables were described as numbers and percentages.

Results

In total, 15 patients underwent HoLEP from April 2022 to December 2022 in a single center. The mean age of the patients was 68.26 (±8.10) years old and the mean prostate volume was 108.6 (±20.04). The mean BMI was 29.5 (±4.25). In detail, the mean height was 1.74 (±0.06) m and the average weight was 89.5 (±10.31) kg [Table 1].

All the operations were successfully completed, while in one patient further hemostasis with monopolar electrocautery was conducted. The average enucleation time was calculated to be 47.13 (±8.44) min, while the morcellation phase was completed in a mean time of 29.8 (±5.35) min. No major complications were noticed. The average hemoglobin drop was 1.4 (±0.69) g/dL, while transfusion was not needed in none of the participants [Table 2].

The mean catheterization time was estimated to be 1.42 (±0.97) days. Two of the patients presented

Table 1: Demographic data of included patients

Patient number	Age (years)	Height (m)	Weight (kg)	BMI (kg/m^2)	Prostate volume
1	68	1.81	82	25.03	95
2	71	1.67	104	37.29	112
3	64	1.79	110	34.33	145
4	52	1.72	89	30.08	87
5	63	1.74	82	27.08	94
6	64	1.69	77	26.96	141
7	59	1.65	89	32.69	127
8	67	1.75	91	29.71	89
9	80	1.79	82	25.59	105
10	79	1.68	75	26.57	101
11	72	1.73	106	35.42	93
12	76	1.72	79	26.7	87
13	61	1.67	96	34.42	99
14	69	1.86	91	26.3	134
15	79	1.81	90	24.47	120
Mean±SD	68.26±8.10	1.74±0.06	89.5±10.31	29.5±4.25	108.6±20.04

BMI: Body mass index, SD: Standard deviation

Table 2: Perioperative outcomes

Patient number	Enucleation time (min)	Morcellation time (min)	Complications	Preoperative Hgb (g/dL)	Postoperative Hgb (g/dL)	Hgb drop	Postoperative hospitalization time (days)	Reason of the hospitalization prolongation
1	49	25	No	14	12.7	1.3	1	-
2	38	37	No	15.8	14.5	1.3	1	-
3	51	35	No	14.5	13.5	1	1	-
4	68	27	Persistent hemorrhage	15.3	12.7	2.6	2	Persistent hematuria
5	45	21	No	14.8	13.7	1.1	1	-
6	35	33	No	13.5	12.4	1.1	1	-
7	37	32	No	15	13.1	1.9	2	Retention after 1st TWAC
8	46	31	No	14.6	13.5	1.1	1	-
9	50	24	No	15.9	14.7	1.2	1	-
10	57	28	No	14.3	12.8	1.5	5	Postoperative fever
11	42	30	No	13	12.2	0.8	1	-
12	47	24	No	12.5	12.2	0.3	1	-
13	53	26	No	16.2	15.4	0.8	1	-
14	48	39	No	15.4	12.7	2.7	2	Retention after 1st TWAC
15	41	35	No	14.6	12.3	2.3	2	Persistent hematuria
Mean±SD	47.13±8.44	29.8±5.35		14.63±1.06	13.22±0.98	1.4±0.69	1.53±1.06	

Hgb: Hemoglobin, SD: Standard deviation, TWAC: Trial without catheter.

persistent hematuria and the catheter was removed on the 2nd postoperative day. Two of the patients presented postoperative retention after the catheter removal and the urethral catheter was placed for one more day when the TWOC was successful. In addition, one of the patients presented postoperative fever after TWOC and the hospital stay was prolonged. The average postoperative hospitalization time was 1.53 (±1.06) days. The patients' follow-up revealed that Qmax increased by an average value of 15.67 (±4.29) and IPSS decreased by an average value of 14.67 (±3.46) at the 3-month follow-up. In addition, the mean percentage of adenomas removed was 74.4% [Table 3].

Discussion

The lasers' hemostatic properties have led to a large implementation of them in the field of urology.[11] EEP techniques have been gradually enriched since the introduction of laser devices as a therapeutic option for BPH. In the current study, we present our experience, surgical and functional outcomes after the performance of 15 HoLEP cases with a sphincter preservation technique using a high-power laser device. All the operations were completed uneventfully, while the patients underwent a 1-month and 3-month follow-up for the observation of their functional status after the surgery.

The first laser enucleation approach with the combination of morcellation has been presented by Fraundorfer and Gilling in 1998.[12] The authors presented the 3-lobe technique in 14 patients. Over the years, the evolution of laser devices and the adaptation of the EEP have contributed to the development of different techniques, while the original one is continuously evolving.[7] During the last decade, the *en bloc* approach has gained popularity and is enriched with numerous modifications, due to the fact that the surgical plane is recognizable with safety, the sphincter preservation can be ensured from the first steps of the operation and the residual volume of prostatic adenoma is minimized.[10,13,14]

The rapid evolution of laser devices with the addition of thulium laser devices in the armamentarium of endourologists is strongly associated with the growing implementation of EEP. Holmium laser is the most investigated one regarding its properties, efficacy, and safety. The comparison between thulium and holmium has always been a controversial topic among researchers. Nevertheless, the current literature demonstrates that both approaches present comparable results in terms of EEP regarding symptom relief and postoperative voiding characteristics according to the meta-analysis presented by Hartung *et al*.[15] The authors observed that Thulium Laser Enucleation of the Prostate (ThuLEP) seems to be slightly superior to HoLEP in terms of hemorrhage and incontinence rate. Thulium fiber laser (TFL) technology is related to more efficient properties in terms of

Table 3: Preoperative and postoperative evaluation

Patient number	Preoperative Q_{max} (mL/s)	Postoperative Q_{max} (mL/s) (3-month follow-up)	Q_{max} increase	Preoperative IPSS	Postoperative IPSS (3-month follow-up)	IPSS decrease	Preoperative prostate volume	Postoperative prostate volume (histopathological repost)	Percentage of adenoma removed (%)	Stress incontinence (pads/day)
1	6	17	11	26	12	14	95	63	66.3	0
2	5	21	16	24	7	17	112	75	67	0
3	8	26	18	20	5	15	145	102	70.3	0
4	5	25	20	25	4	21	87	71	81.6	0
5	7	21	14	26	11	15	94	70	74.5	0
6	10	19	9	24	10	14	141	98	69.5	0
7	11	23	12	21	10	11	127	105	82.7	0
8	8	26	18	26	7	19	89	70	78.7	0
9	9	25	16	26	12	14	105	76	72.4	0
10	7	21	14	24	6	18	101	83	82.2	0
11	2	22	20	19	8	11	93	59	63.4	0
12	4	27	23	23	8	15	87	62	71.3	0
13	12	20	8	21	10	11	99	77	77.8	0
14	5	23	18	21	13	8	134	102	76.1	0
15	7	25	18	24	7	17	120	98	81.7	0
Mean±SD	7.06±2.71	22.73±2.91	15.67±4.29	23.33±2.38	8.67±2.72	14.67±3.46	108.6±20.04	80.73±16.10	74.4	

IPSS: International prostate symptom score, SD: Standard deviation

hemostasis due to the pulsed wavelength delivery and the shallower tissue penetration.[16] The theoretical basis behind TFL Enucleation of the Prostate (ThuFLEP) can be confirmed by Enikeev *et al*.[17] The authors conducted a randomized controlled trial including 103 patients, comparing the efficiency of ThuFLEP in comparison to TURP for smaller prostate glands. They demonstrated that ThuFLEP is superior regarding the percentage of adenomas removed, postoperative complication rate, and hospitalization time.[19] Thus, the method of BPH surgical management should be based on local conditions and the surgeon's convenience.

In the current study, we presented our early outcomes of HoLEP with Quanta Litho Cyber Ho 150 W™ including 15 patients. Pirola *et al*.[20] presented a comparative study with 234 patients. The authors conducted a retrospective matched-pair analysis of 117 patients who underwent HoLEP and 117 patients that underwent ThuLEP for the treatment of BPH. The median enucleation time was 70.5 (58–104 interquartile range [IQR]) min and 70 (58.0–87.3 IQR) min for the HoLEP and the ThuLEP group, respectively, while the morcellation time was 11.5 (8–16 IQR) min and 12.12 (9.5–14.5 IQR) min for the same groups. In our study, the enucleation duration was 47.13 ± 8.44 min, while the morcellation needed a mean time of 29.8 ± 5.35 min to be completed. In addition, the authors reported an intraoperative complication rate of 5.7% for the HoLEP group and 7% for the ThuLEP group, while our intraoperative complication rate was 1.5%. The hemoglobin drop was calculated to be 0.9 g/dl (ranging from 0.3 to 1.67) and 0.5 g/dl (from 0.3 to 1.1) for the holmium and the thulium groups, respectively, while the average hemoglobin drop in our study was 1.4 (±0.69) g/dL. The IPSS score and Q_{max} evaluation did not present differences between the two studies. In addition, in the current study, it was calculated that 74.4% of the adenoma was removed, ranging between 63.4% and 82.7%.

The current study presented 15 cases of HoLEP. The main advantages of the technique have already been mentioned. Nevertheless, our clinical study has also some limitations. First of all, the surgeon that performed the operations is an experienced one having completed more than 100 cases. In addition, the number of cases is restricted, but the safety and efficacy of this technique are underlined by our results. Thus, we believe that the presented data are important for the evaluation of prostatic adenoma enucleation with the use of a high-power laser device.

Conclusion

Our initial experience and early outcomes of the use of Quanta Litho Cyber Ho 150 W™ (Quanta System, Samarate, Italy) in HoLEP were presented. Majority of the cases were completed successfully, without major complications or significant blood loss.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Evaluation of Initial 24-core Transrectal Prostate Biopsy on the Detection of Significant Prostate Cancer and High-grade Prostatic Intraepithelial Neoplasia

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Abstract

Purpose: The purpose of the study was to assess the diagnostic value of an initial 24-sample transrectal ultrasound-guided (TRUS) prostate biopsy protocol compared to the 10-core technique. **Materials and Methods:** We retrospectively reviewed the prostate biopsy database of consecutive men undergoing prostate biopsies under local anesthesia using the 10 (Group A) and 24 (Group B) protocols. Men were stratified according to biopsy protocol and prostate-specific antigen (PSA) levels. Exclusion criteria were age = 75 years and PSA >20 ng/mL. The Mann–Whitney *U* and Fisher's exact test were used for statistical analysis. **Results:** Between November 2018 and August 2020, 169 men underwent TRUS prostate biopsies. Group A (10-cores) consisted of 105 (62.13%) men and Group B (24-cores) included 64 (37.86%) men. The overall prostate cancer detection rate was 41.05% and 36.72% in Groups A and B, respectively ($P = 0.48$). An overall 9.8% increase in Gleason 7 detection rate was found in Group B ($P = 0.24$). The high-grade prostatic intraepithelial neoplasia (HGPIN) detection rate in men with negative initial biopsies was 15.54% and 35.55% in Groups A and B, respectively ($P < 0.001$). In patients with PSA <10 ng/mL, the 24-core technique increased Gleason 7 detection rate by 13.4% ($P = 0.16$) and HGPIN by 23.4% ($P = 0.0008$), compared to the 10-core technique. The 24-core technique increased the concordance between needle biopsy and prostatectomy specimen compared to the 10-core technique ($P < 0.002$). **Conclusions:** The initial 24-core prostate biopsy protocol did not show any benefit in the detection of prostate cancer compared to the 10-core technique. However, it improved the HGPIN detection and the correlation between biopsy results and radical prostatectomy Gleason score in men with lower PSA levels.

Keywords: *Biopsy, Gleason score, prostatic intraepithelial neoplasia, prostatic neoplasm*

Introduction

As recommended by Hodge *et al.*,[1] systematic transrectal ultrasound-guided (TRUS) prostate biopsies is the principal method of diagnosing prostate cancer. Several studies have demonstrated that the traditional sextant technique may miss 15%–31% of cancers and additional sampling from the peripheral zone increases the diagnostic yield of prostate biopsies.[2-5] Although there is still a matter of debate regarding the optimal number of cores taken at the initial prostate biopsy, several reports have shown that extended biopsy protocols involving >10-core have improved the diagnostic accuracy of clinically significant prostate cancer, especially in patients with bigger glands[6,7] and also improved the concordance of Gleason scores of needle biopsies and prostatectomy specimens.[8]

The aim of the present study was to evaluate the incidence of prostate cancer, high-grade prostatic intraepithelial neoplasia (HGPIN), and perineural infiltration rates in men who had initial 24-core biopsies. The results were then compared with a similar group of men who had an initial 10-core prostate biopsy protocol. Men were categorized into different subgroups according to prostate-specific antigen (PSA) levels. We also evaluated the ability of the initial saturation biopsy scheme to improve the prediction of the radical prostatectomy Gleason score compared to the 10-core technique.

Materials and Methods

We retrospectively reviewed the concurrently maintained database of consecutive men who underwent TRUS prostate biopsies at one

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referral center. Indications for biopsy were abnormal digital rectal examination and elevated age-specific PSA levels. The 10 cores and saturation (24 cores) biopsy protocols were used as initial techniques by two staff members of the department. We used a biplane 10 MHz transrectal probe (Pro-Focus 2202™, BO-Medical, Denmark) with the capability of real-time three-dimensional imaging. A 20 cm 18G Chiba biopsy needle was used through a Pro-Mag™ automated ultra biopsy gun (Angiotech Vancouver, BC, Canada). Prostate biopsies were done with periprostatic nerve block using 5 mL 0.5% marcaine mixed with 5 mL 1% lidocaine administered at the prostate base where the prostate sensory nerves enter the gland. One dose of ciprofloxacin as standard antibiotic prophylaxis was given to all patients before biopsy and written informed consent was obtained from all patients.

Men were categorized into two groups according to biopsy protocol and PSA levels. For Group B (24 cores), the five sectors biopsied on each side were lateral base (2), lateral mid-zone (3), apex (3), parasagittal mid-zone (2) and parasagittal base (2) as shown in Figure 1. Men in Group A (10 cores), had one biopsy core obtained from each of the same sectors.

Men = 75 years old, with PSA <2.5 ng/mL and/or >20 ng/mL and those who were previously biopsied, were excluded from the analysis. Biopsy findings from both groups were compared regarding prostate cancer and HGPIN detection rates. Repeat saturation prostate biopsies were performed in 39 men from both groups with HGPIN in the initial biopsy. The concordance of Gleason score in the needle biopsy and prostatectomy specimens from both groups was also compared. Complications in both groups were recorded and compared.

Statistical analysis

Results were analyzed using either the Mann–Whitney *U*-test for continuous variables or Fisher's exact test for categorical variables.

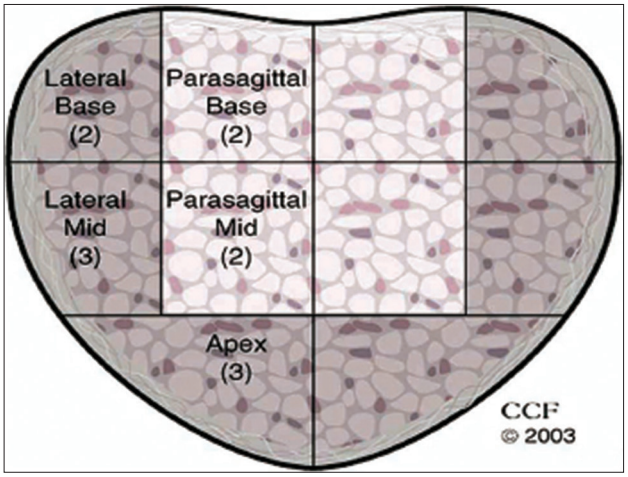

Figure 1: Template showing the location of cores obtained in 24-core needle transrectal ultrasound biopsy. In the 10-core biopsy protocol, one core was obtained from each of the same sectors

Results

Between November 2018 and August 2020, 169 men underwent TRUS prostate biopsies. Group A (10-core) consisted of 105 (62.13%) men and Group B (24-core) included 64 (37.86%) men. Overall, 169 men (clinical stage T1c, T2), were suitable for analysis. Both groups were comparable in terms of age, PSA, and prostate volumes. The patient's demographics are summarized in Table 1.

The overall prostate cancer detection rate was 39.09% and 34.55% in Groups A and B, respectively (P = 0.43). Table 2 shows prostate cancer detection rates according to biopsy protocol and PSA levels. An overall 9.8% increase in the Gleason 7 score was found in Group B compared to Group A (P = 0.24). There was no difference in perineural infiltration rate between both groups (P = 0.79). At a PSA range between 2.6 and 9.9 ng/mL, the 24-core technique showed a nonstatistically significant increase in the Gleason 7 detection rate compared to the 10-core technique (P = 0.16). Table 3 shows Gleason score detection rates stratified according to biopsy protocol and PSA values.

The overall HGPIN detection rate in men with negative initial prostate biopsies was 15.54% and 35.55% in Groups A and B, respectively (P < 0.001). In Group B and at a PSA range between 2.6 and 9.9 ng/mL, the overall HGPIN detection rate was increased by 23.4% (P = 0.0008), compared to Group A. Multifocal HGPIN detection was 8.7% and 25.4% in Group A and B, respectively (P < 0.001). After a follow-up of 6–13 months, prostate cancer was subsequently detected in 8% and 74% at repeat saturation biopsies of patients with isolated and multifocal HGPIN, respectively. Table 4 shows HGPIN

Table 1: Clinical characteristics of patients

Clinical parameters	10-biopsy protocol (*n*=243)	24-biopsy protocol (*n*=136)	*P*
Age (years)	65.4±6.4	66.1±7.2	0.18
PSA (ng/ml)	6.2±4.3	6.2±3.9	0.20
Prostate volume (ml)	42.5±5.2	46.7±8.3	0.16
DRE (+)	21%	8.82%	0.028 NSS

DRE: Digital rectal examination, PSA: Prostatic specific antigen

Table 2: Prostate cancer detection rates according to biopsy protocol and PSA values

	% Pca Detection		*P*, Fisher's exact test two tailed
	10-biopsy protocol	24-biopsy protocol	
PSA (ng/ml)			
2.6–9.9	37.05% (73/197)	33.66% (34/101)	0.61
10-20	47.8% (22/46)	37.1% (13/35)	0.37
2.6-20	39.09% (95/243)	34.55% (47/136)	0.43

PSA: Prostatic specific antigen

Table 3: Gleason score stratified rates according to biopsy protocol and PSA values

Gleason score	6	7	8	9
Biopsy cores	10 %	10 %	10 %	10%
	24 %	24 %	24 %	24 %
2.6-9.9 ng/ml	49.3 (36/73)	21.9 (16/73)	4.1 (3/73)	8.2 (6/73)
	41.2 (14/34)	35.3 (12/34)	11.8 (4/34)	2.9 (1/34)
10-20 ng/ml	63.6 (14/22)	59.0 (13/22)	18.2 (4/22)	9.0 (2/2)
	46.15 (6/13)	53.8 (7/13)	15.4 (2/13)	7.7 (1/13)

PSA: Prostatic specific antigen

Table 4: High grade prostatic intraepithelial neoplasia (HGPIN) detection rates in biopsy negative patients stratified according to biopsy protocol and PSA values

	% HGPIN Detection		*P*, Fisher's exact test two tailed
	10-biopsy protocol	24-biopsy protocol	
PSA (ng/ml)			
2.6–9.9	16.9 (21/124)	40.3 (27/67)	0.0008
10-20	8.33 (2/24)	21.73 (5/23)	0.24

detection rates at different PSA levels stratified according to biopsy protocols.

Of the subset of 62 patients from both groups who underwent radical prostatectomy and were available for analysis, 13.7% had clinically insignificant cancer (maximal tumor dimension of 1.0 cm or less, Gleason sum 6 or less, and organ-confined disease at radical prostatectomy). In men who underwent 10 core biopsies, the overall rate of Gleason score upgrading after radical prostatectomy was 42.9% compared to 26.5% if 24 cores were taken ($P < 0.002$). No patients in the saturation needle biopsy group had a discrepancy of more than one Gleason unit in grade in the biopsy and surgical specimens. There were no differences in complication rates between both groups. Febrile urinary tract infections were recorded in three men from Group B and two men from Group A. While rectal bleeding necessitating admission was recorded in two men from Group B, there was no significant difference in patient discomfort between both groups.

Discussion

Prostate cancer screening has currently increased the importance of prostate biopsy in urological practice and the detection of prostate cancer. Systemic transrectal needle biopsy of the prostate is the standard practice to detect the clinical stage and grade of disease, but controversy still exists about the optimal number of cores and the significance of HGPIN on the first biopsy, and how the biopsy results will improve the prediction of the prostatectomy Gleason score. In a review study, Epstein–Herawi recommended no-repeat biopsies within the 1st year following the diagnosis of HGPIN because the 24% median risk of prostate cancer diagnosis following detection of HGPIN was not higher than that of initial biopsy with benign disease.[9] In our study, it was not the presence but the multifocality of HGPIN, which was the strongest predisposing factor for detecting prostate cancer in a subsequent biopsy.

Presti[10] reviewed several studies evaluating several biopsy schemes and suggested that 10–12 core technique is optimal for most men undergoing initial prostate biopsy. Nesrallah *et al*. concluded that extended biopsy, with 14 cores, could improve prostate cancer detection rate compared to the sextant technique.[11] Jones *et al*. noted, although in a small number of patients, that the 24-core technique as an initial strategy did not improve cancer detection.[12]

While many studies show that saturation biopsy improves prostate cancer detection in patients with suspicious findings in a first negative biopsy, it does not seem to increase the cancer detection rate as an initial technique. Our findings are in agreement with these reports, as the 24-core initial biopsy technique did not improve the overall prostate cancer detection rate compared to the 10-core technique. In our study, men with PSA <10 ng/mL who received an initial 24-core biopsy did not have a statistically significant increase in the Gleason 7 detection rate when compared to 10-core protocol at the same PSA level. Furthermore, there was no difference in Gleason 8 and 9 detection rates between both biopsy protocols.

Scattoni *et al*. also showed that the 18-core technique as an initial strategy demonstrated a higher cancer detection rate, although not statistically significant, than the 12-core protocol in men with PSA <10 ng/mL, but they did not find any difference in the Gleason score.[13] In a recent study, Scattoni *et al*. showed that both the number and site of cores have a great impact on prostate cancer detection and concluded that cancer detection rates increased with the increasing number of cores.[14]

There are only a few reports in the literature that address the influence of increased biopsy sampling on the detection rate of HGPIN and the cancer risk associated with it in subsequent biopsies. Epstein and Potter reported no relationship between the number of cores sampled and the incidence of HGPIN in needle biopsy.[15]

However, Moore *et al*. found an incidence of 22% in HGPIN on the first saturation biopsy. This finding was confirmed in our study, where the HGPIN detection rate of 35.55% in men who had initial saturation biopsies was one of the highest reported in the literature.[16]

Several studies have reported varying results for the positive predictive value of HGPIN as a single finding for prostate cancer detection in subsequent biopsies.[17,18] In the present study, the cancer detection rate was significantly higher in patients with multifocal HGPIN in the initial biopsy than in those with unifocal HGPIN ($P = 0.001$). The majority of patients (78%) with multifocal HGPIN

on initial saturation biopsy were diagnosed with prostate cancer on repeat saturation biopsy, of which 11.8% had clinically insignificant cancer in prostatectomy specimens. These findings have been confirmed by other studies where the multifocality of HGPIN is an independent risk factor of prostate cancer in subsequent biopsies.[19]

Recently, few reports have proved that the extended prostate biopsy scheme, when compared to the sextant technique, significantly improves the correlation between needle biopsy and prostatectomy Gleason score, and reduces the risk of upgrading to a worse Gleason group at prostatectomy.[20,21] In our study, Gleason score upgrading was significantly higher in the 10-core protocol when compared to the saturation technique. This finding is important since most prostate cancer cases are now detected at an early stage and at a low PSA level. Leite *et al*. also showed that extended prostate biopsies in men with PSA <4 ng/mL increased the accuracy in tumor volume, Gleason score, and stage when compared with higher PSA values.[22]

No difference in the detection of clinically insignificant cancer in radical prostatectomy specimens was observed between both biopsy protocols. In addition to its interesting results, the present study presents some limitations with the most obvious being that we do not know how many cancers were missed with either the 24 or 10-core technique. Thus, our study is influenced by verification bias because we cannot define the real diagnostic accuracy of our biopsy schemes. Another limitation is that this study is a retrospective audit with a nonrandomized design.

The present study did not show a real benefit for the saturation biopsy protocol as an initial technique for the detection of prostate cancer. However, it did show that an initial 24-core technique increased the detection of multifocal HGPIN and improved the concordance of Gleason grading between needle biopsy and radical prostatectomy specimen, which is crucial in therapeutic decision-making based on needle biopsy.

Conclusions

Our findings add to the growing evidence in the literature that an initial saturation (24-core) prostate biopsy protocol does not improve the overall cancer detection rate compared to the 10-core technique. Although the 24-core prostate biopsy technique improved the sensitivity of HGPIN detection, especially in men with PSA levels <10 ng/mL, it cannot be justified as the standard initial biopsy technique. Patients with multifocal HGPIN on initial saturation biopsy certainly warrant repeat saturation biopsy since the great majority of them will be later diagnosed with prostate cancer. Given the fact of its safety profile, the 24-core prostate biopsy protocol could probably be proposed as the initial technique for a selected group of patients, such as younger men with lower PSA levels who are candidates for curative treatment, or younger patients who have opted for active surveillance. Further studies are certainly needed in this field.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

A Randomized Study of b3 Agonists versus Anticholinergics Administration in Patients with Multiple Sclerosis and Lower Urinary Tract Dysfunction

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Abstract

Introduction and Objective: Multiple sclerosis (MS) is the most frequent autoimmune demyelinating disease of the central nervous system usually affecting lower urinary tract function. In the present study, we compare the efficacy and safety of either a b3 agonist (mirabegron) or anticholinergics in treating MS patients with lower urinary tract dysfunction (LUTD) and assess the LUTD symptom improvement. **Evidence Acquisition:** A multi-center, single-blinded, comparative study was designed, including MS patients with LUTD. Patients were administered either mirabegron or anticholinergics in combination with standard MS treatment. All cases underwent clinical examination and completed urination diaries and validated questionnaires (Neurogenic Bladder Symptom Score and MS International Quality of Life). Furthermore, urine test analysis, as well as abdominal ultrasound imaging examination, was performed. Data on several clinical and imaging parameters were collected between the two groups at the first visit and after 3 months of treatment. **Evidence Synthesis:** A total of 61 patients with LUTD participated in the survey. An improvement regarding LUTD was noted in all patients. However, no statistical difference was recorded between the mirabegron and the anticholinergic group. Medical treatment was well tolerated, and no patient discontinued medication due to side effects. **Conclusions:** Both mirabegron and anticholinergic therapy can be administered for LUTD in MS patients. In terms of drug efficacy, no statistical difference was noted between the two cohorts at 3 months.

Keywords: *Anticholinergics, b3 agonists, lower urinary tract dysfunction, multiple sclerosis*

Introduction

Multiple sclerosis (MS) is the most frequent autoimmune demyelinating disease of the central nervous system (CNS), characterized by a wide range of clinical presentation and evolution.[1] Pathology examination of MS lesions highlights the presentation of the MS plaques and lymphocyte infiltrations, which can preexist for years before the onset of clinical symptoms. Their exact location profiles unique features of lower urinary tract dysfunction (LUTD). Most patients suffer from neurogenic detrusor overactivity (NDO) and recurrent urinary tract infections (UTIs).[2]

The prevalence of LUTD symptoms in MS patients ranges from 6.9% to 95%. The symptoms occur on average 6 years after the onset of MS, and almost all MS patients will experience LUTD within 10 years or more of MS onset.[3] As aforementioned, NDO and recurrent UTIs are often diagnosed in MS patients. NDO symptoms include increased frequency, urgency, incontinence, and nocturia and many patients deal with complications arising from LUTD, such as urinary incontinence and recurrent UTIs. Among the various symptoms of MS, the neurogenic dysfunction of the lower urinary tract contributes notably to reducing the quality of patients' life.[4] Moreover, such symptoms are often underestimated by attending physicians. As a result, detailed recording and treatment of LUTD are of great importance to prevent complications and offer a better quality of life (QoL).[5]

Currently, the treatment of NDO is based on two different agents, b3 agonists and anticholinergics. However, there is a lack of trials comparing these drugs in the MS patients' population. In the present study, we compared the efficacy and safety of treating MS patients with LUTD using either b3 agonist (mirabegron) or anticholinergics.

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Materials and Methods

Inclusion/exclusion criteria

This is a multi-center, comparative study, including MS patients with LUTD treated with either b3 agonist or anticholinergics. Patients were randomized 1:1 to b3-agonist and anticholinergics while blinding of the data collectors and outcome managers were conducted throughout the study (single-blinded study). Eligibility criteria included adults ≥18 years old, native speakers of the Greek language, who were diagnosed with MS of various types and severity of neurological disabilities, according to Poser *et al*.[6] and McDonald *et al*.[7] criteria for >6 months.

Patients with urologic surgery within the past year, a history of radiotherapy in the pelvis, a recent change of health situation, a change of MS treatment for their symptoms, or an active UTI within the past month were excluded from the study. Patients with contraindications to treatment with either mirabegron or anticholinergics were excluded from the study. Patients with impaired cognition unable to fill in the questionnaires, as well as patients with a main diagnosis other than MS, were also excluded from the study.

Evaluation and treatment

An extensive medical history was recorded while all patients underwent thorough clinical examination, including neurological and digital rectal examination. In addition, urine test analysis and ultrasound imaging examination were undertaken. Cases diagnosed with either upper tract dilatations or clinically significant postvoid residual (PVR) >150 ml were recorded. Meanwhile, all patients completed urination diaries for at least 3 consecutive days and specific validated questionnaires such as the MS International QoL (MusiQoL) and Neurogenic Bladder Symptom Score (NBSS) questionnaires.[8,9] Both questionnaires are validated in the Greek language.[10,11]

After a median of 20 days (range 16–25) from their first evaluation, participants were re-examined and either a b3 agonist (mirabegron) or an anticholinergic (solifenacine or fesoterodine) were administered. The choice of which anticholinergic drug to be used was random.[12] Furthermore, two different anticholinergic subgroups were created based on the starting dose of medication. The choice of the starting dose of either medication was based on the initial evaluation of each patient considering several parameters like the patient's age and known comorbidities. Charlson Comorbidity Index was used in our study to classify patients with mild, moderate, and severe comorbidities and focus on patient safety profiles.[13] Patients with mild-to-moderate symptoms or older patients with known severe comorbidities were administered the minimum starting dose, while patients with severe symptoms and a safe medical history were initiated with the maximum dose.

Treatment evaluation was performed 3 months after the first visit. Patients underwent clinical and imaging examinations, while dose escalation was performed in some of them. Dose escalation was decided in patients who were unsatisfied with their LUTD improvement without any contraindications of increasing the drug dose.

Study endpoints

The primary outcome was the evaluation of the LUTD symptom improvement between patients treated with b3 agonist and anticholinergic medication. At this point of view, symptom-related questionnaires were used. Secondary endpoints included the rest of the parameters examined, such as urinary test results and imaging findings.

Statistical analysis

Clinical and imaging examination data were collected. The scores of the two questionnaires, as well as ultrasounds' reports, PVR, urine cultures, and the urination diaries results, were recorded before and after (at 3 months) medication treatment. Statistical analysis of the results was performed using the SPSS version 16 (SPSS Inc., Chicago, IL, USA) statistical package with $P < 0.05$ considered significant. Furthermore, the Chi-square and *t*-test were used, as appropriate.

Results

A total of 61 patients enrolled in the study and were classified into two groups. Group A included 31 patients and Group B consisted of 30 patients treated with mirabegron 25/50 mg and solifenacin 5/10 mg or fesoterodine 4/8 mg, respectively. The mean age of patients included in Group A was 51.2, while patients in Group B had a mean age of 50.7 years. Regarding medication dosage, 16 patients received mirabegron 25 mg and 15 patients received mirabegron 50 mg. In Group B, 7 patients received solifenacin 5 mg and 8 of them received solifenacin 10 mg. Fesoterodine 4 mg was administered to 6 cases and 9 of them received fesoterodine 8 mg. Most of the participants (46) had no previous medical treatment for LUTD symptoms [Table 1].

During reevaluation at 3 months, 12 patients of Group A upregulated their medication from mirabegron 25 to mirabegron 50 mg. On the other hand, 7 patients of Group B receiving solifenacin increased their dose from 5 mg to 10 mg and while 1 participant receiving fesoterodine 4 mg was given fesoterodine 8 mg.

Regarding our primary endpoint, a significant improvement in patients' symptoms was recorded [Table 2], with urgency episodes observed less frequent (6.3–2.8 Group A, 6.3–3.5 Group B). Similar improvement was recorded in both questionnaires used for patients' QoL evaluation. MusiQoL score was reduced from 65.2 to 50.5 in Group A and from 65.4 to 47.6 in Group B. Similarly, the NBSS score was reduced from 26.1 to 20.1 in Group A and from 26.8 to 19.9

in Group B [Table 3]. However, no statistical difference was noted between Group A and Group B medication treatment. Moreover, there was no difference from their baseline in terms of secondary endpoints, such as PVR and upper tract

Table 1: Patient baseline characteristics

	Mean (range)		*P*
	Group A patients treated with b3 agonist (*n*=31)	**Group B patients treated with anticholinergics (*n*=30)**	
Age (years)	51.2 (27–80)	50.7 (26–69)	0.1
Male gender patients, *n* (%)	14 (45.16)	9 (30)	0.16
Years since MS diagnosis	11.2 (2–40)	11.5 (1–39)	0.44
Years since initiation of LUTD	6 (1–19)	6.2 (1–18)	0.149
Previous treatment patients, *n* (%)	11 (35.5)	10 (33.3)	0.385
Bladder management			
Indwelling catheter	0	1	
Condom catheter	0	0	
Intermittent catheter	5	5	
Spontaneous voiding	26	27	
PVR >150 mL patients, *n* (%)	6 (19.35)	8 (26.66)	0.173
US dilatations (+) patients	1 (3.2)	2 (6.6)	0.08
Patients with (+) urine culture, *n* (%)	3 (9.67)	4 (13.3)	0.3
MusiQoL score	65.2 (33–109)	65.4 (19–99)	0.446
NBSS score	26.1 (6–58)	26.8 (1–57)	0.34
Daily fluid intake (mL)	1550 (550–3900)	1450 (700–2810)	0.074
Daily urgency episodes	6 (0–25)	6 (0–16)	0.42
Daily number of urinations	11 (4.5–25)	10.7 (3–16)	0.26
Urination volume (mL)	160 (60–350)	155 (50–350)	0.33

MS: Multiple sclerosis, NBSS: Neurogenic Bladder Symptom Score, MusiQoL: MS International Quality of Life, PVR: Postvoid residual, US: Ultrasound, LUTD: Lower urinary tract dysfunction

Table 2: Comparison of the results of the two groups after treatment

	Mean (range)		*P*
	Group A patients treated with b3 agonist (*n*=31)	**Group B patients treated with anticholinergics (*n*=30)**	
Patients with (+) urine culture (%)	0	0	0.5
MusiQoL score	50.5 (24–86)	47.6 (16–71)	0.4
NBSS score	20.1 (6–44)	19.9 (0–42)	0.24
Daily urgency episodes	2.5 (0–9.8)	3.1 (0–10.1)	0.078
Daily number of urinations	8.1 (5.5–18)	8.6 (5–11.5)	0.43
Urination volume (mL)	209 (68–400)	200.1 (75–325)	0.25

NBSS: Neurogenic Bladder Symptom Score, MusiQoL: Multiple Sclerosis International Quality of Life

Table 3: Patient data before and after treatment

	Group A patients treated with b3 agonist (*n*=31)		*P*	**Group B patients treated with anticholinergics (*n*=30)**		*P*
	Baseline	**3 months**		**Baseline**	**3 months**	
PVR >150 mL patients, *n* (%)	6 (19.35)	4 (12.9)	0.19	8 (26.66)	5 (16.6)	0.23
US dilatations patients, *n* (%)	1 (3.2)	1 (3.2)	0.5	2 (6.6)	2 (6.6)	0.5
Patients with (+) urine culture, *n* (%)	3 (9.67)	0	0.05	4 (13.3)	0	0.02
MusiQoL score, mean (range)	65.2 (33–109)	50.5 (24–86)	<0.001	65.4 (19–99)	47.6 (16–71)	<0.001
NBSS score, mean (range)	26.1 (6–58)	20.1 (6–44)	0.023	26.8 (1–57)	19.9 (0–42)	0.0013
Dairy fluid intake (mL), mean (range)	1550 (550–3900)	1692 (1000–3670)	0.36	1450 (700–2810)	1537 (720–2500)	0.28
Dairy urgency episodes, mean (range)	6 (0–25)	2.5 (0–9.8)	<0.001	6 (0–16)	3.1 (0–10.1)	<0.001
Dairy number of urinations, mean (range)	11 (4.5–25)	8.1 (5.5–18)	<0.001	10.7 (3–16)	8.6 (5–11.5)	<0.001
Urination volume (mL), mean (range)	160 (60–350)	209 (68–400)	<0.001	155 (50–350)	200.1 (75–325)	<0.001

NBSS: Neurogenic Bladder Symptom Score, MusiQoL: Multiple Sclerosis International Quality of Life, PVR: Postvoid residual, US: Ultrasound

dilatations, between patients treated either with mirabegron or anticholinergics. Finally, both medical regimens were well-tolerated, as no patient discontinued either medication due to side effects and no major side complications were reported.

Discussion

The lower urinary tract is quite often affected by MS as well as other neurological diseases. Treatment goals consist of the protection of the upper urinary tract, the avoidance of any urinary complications, along with the improvement in patients' QoL. In this setting, combination therapy, including oral drugs and intermittent catheterization, consist of an often applied treatment approach.[1] In medical treatment, anticholinergics are the most commonly prescribed regimen in patients suffering from neurological disorders, as their efficacy and safety profile are well established.[12]

In the MS population, data suggesting anticholinergics as a treatment option were assessed in a Cochrane Systematic Review published in 2009. Based on the review, no evidence of significant improvement in LUTD in patients with MS was recorded. In addition, a high incidence of adverse events was noted, as well as a high withdrawal rate due to adverse effects.[13] On the other hand, a double-blind, randomized, and controlled trial was conducted comparing oxybutynin and solifenacin, to a placebo in patients with NDO. Based on the study, anticholinergic medication significantly improved urinary function and QoL.[14] Lust but not least, a retrospective cohort study by Goodson *et al*., including 567 patients with MS, evaluated the comparative effectiveness of novel anticholinergic agents. Both solifenacin and fesoterodine recorded better outcomes compared to tolterodine.[15] To maximize efficacy, the combination of anticholinergics or dose escalation may be used, with the increased risk of side effects to be taken into account.[16]

Although no superiority of any anticholinergic agent over another is proved in patients suffering from MS, a difference in safety profile seems to occur.[12,13] Less side effects are present at newer anticholinergic drugs such as solifenacin, tolterodine, and fesoterodine and therefore are preferred over older agents.[17] The most common side effects associated with anticholinergic oral use are dry mouth and constipation. Patients' risk factors of experiencing side effects are elderly and consumption of multiple medications.[17,18] Moreover, regimens crossing the blood–brain barrier (BBB) could lead to CNS side effects such as cognitive impairment. In cases with previous loss of cognitive level, drugs that do not cross the BBB, such as darifenacin, trospium chloride, and fesoterodine, are preferred.[19]

In 2012, the Food and Drug Administration approved the first nonanticholinergic oral medication, mirabegron, to treat patients with overactive bladder (OAB) symptoms. Mirabegron consists of a beta-3-adrenergic receptor agonist that stimulates beta-3 receptors, causing smooth muscle relaxation in the bladder.[20] Literature report mirabegron as a safe treatment option with few side effects and a low incidence of CNS effects.[21-23] Even though the safety and efficacy of mirabegron are well established in patients with OAB, in cases of neuro-urological patients, data are limited.[24] In a prospective, multicenter, randomized, double-blind, placebo-controlled study including 78 patients with either spinal cord injury or MS, patients who received mirabegron 50 mg improved both urodynamic variables and patient-reported outcomes.[25] In another randomized, double-blind placebo-controlled Canadian study, the effectiveness of mirabegron was evaluated in patients with spinal cord injury or MS suffering from LUTD and incontinence. The authors demonstrated a nonsignificant trend toward improvement in some urodynamic parameters with mirabegron 50 mg compared to placebo.[26]

Literature also lacks reports on comparing mirabegron with anticholinergics in MS patients. A comparative study by Zachariou *et al*. was conducted, including 60 MS patients with NDO. Patients were randomized to receiving therapy with solifenacin 10 mg/daily, mirabegron 50 mg/daily, desmopressin 120 μg/daily or mirabegron 50 mg/daily, and desmopressin 120 μg/daily. The combination treatment with mirabegron and desmopressin appeared to be the most effective in patients with NDO and MS.[27] Another study by Brucker *et al*. compared the efficacy of solifenacin versus mirabegron medication in previous pharmacotherapy targeting LUTD naïve MS patients. Study concluded that both groups had similar response rates where responsiveness was evaluated with OAB Questionnaire Short Form.[28] In a systematic review by El Helou *et al*., data by seven studies and a total of 302 participants were collected evaluating mirabegron in neurogenic bladder patients. In all cases, mirabegron was administered as a second-line treatment after anticholinergics, and positive results were reported in terms of clinical scores, specifically in storage symptoms.[29]

In the present study, two anticholinergic agents, solifenacin and fesoterodine, were administered and compared with mirabegron in MS population suffering LUTD symptoms.[30] In our knowledge, our study is one of the first studies comparing the efficacy of mirabegron versus anticholinergics in MS patients. Meanwhile, mirabegron was evaluated as a first-line treatment option and not as a second-line medication after anticholinergics. We compared several clinical and imaging parameters, and significant improvement in LUTD was noted in both groups of patients from baseline to 3 months after treatment. To compare the efficacy of the medical treatment, two validated questionnaires regarding QoL were used while a variety of secondary endpoints (urine test, ultrasound results) were recorded. The results of our study are in accordance with literature regarding the efficacy and safety profile of both anticholinergics agents and mirabegron.[31]

Limitations of our study include patient recruitment, variability on regimens dosage as well as the follow-up duration. Patients were recruited only at academic centers in Athens, while patients in more remote areas may need a different approach due to educational, social economic, and cultural differences. On the other hand, the relatively large sample size of 91 patients alleviates these limitations and strengthens the results. To our knowledge, this is one of the first comparative studies comparing the efficacy and safety of b3 agonists and anticholinergics in MS patients suffering from LUTD.

Conclusions

Both mirabegron and anticholinergics are equally efficient in the treatment of LUTD in MS patients and the choice of which drug to use should be based on patient safety profile and comorbidities as no drug proved to be superior in terms of efficacy.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

A Rare Case of Complete Urethral Duplication and Short Review of the Literature

Abstract

Duplication of the urethra is a rare congenital anomaly, predominantly seen in males. Due to the rarity of the condition, there is no fixed consensus regarding the management of these patients. We report the case of a 4-year-old male child who presented with phimosis and balanoposthitis, with the occasional double stream of urine and was incidentally found to have duplication of the urethra. Cystoscopy revealed the duplication to be Effman Type II A-1. No surgical intervention was done for the duplication as the patient was asymptomatic. Our aim is to report this rare case and to enhance the knowledge by reviewing the already existing scanty literature of this rare condition.

Keywords: *Anomalies, complete, duplication, urethral, urogenital*

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Introduction

Duplication of the urethra is an incompletely understood rare congenital abnormality. It can have varying clinical presentations and anatomic variations. They can be associated with other anomalies of the urogenital system and caudal duplication anomalies. The vast majority of these duplications are in the sagittal plane with a dorsal and ventral urethra, with the dorsal epispadiac urethra most commonly noted as being the accessory.[1,2] With few cases reported in the literature, there is no fixed consensus regarding treatment, and it is understood that the treatment must be tailor-made to the individual patient after all risks and benefits are assessed. Here, we report a case of Effman type II A-1[3] urethral duplication, which was incidentally noted when the patient was brought for phimosis and balanoposthitis. Operative intervention was not done as the patient was asymptomatic except for an occasional double stream of urine.

Case Report

A 4-year-old male child was brought by parents with the complaint of phimosis with smegma discharge and intermittent ballooning of prepuce while passing urine. The patient had no complaints of burning micturition, difficulty passing urine, and fever episodes. There was a history of occasional double stream of urine on straining during micturition.

Biochemical investigations were within normal range, and the birth history was insignificant. On examination, tight phimosis with balanoposthitis was present, along with a penoscrotal web and mild dorsal chordee [Figure 1]. Sonography was done, which further revealed a normal left kidney and nonvisualized right kidney. No hydroureteronephrosis was seen, and postvoid residue was normal.

The patient was taken up for circumcision and excision of the penoscrotal web. Intraoperatively, on performing adhesiolysis of the glans, an orthotopic ventral urethra was seen along with a dorsal urethral opening. The ventral urethra was catheterized with an 8 Fr infant feeding tube. The dorsal urethra being smaller, allowed cannulation with a 6 Fr infant feeding tube [Figure 2]. Cystoscopy was performed with a 7Fr integrated scope through the ventral urethral opening, and both urethral openings were seen in the bladder. There was evidence of hemitrigone with a normal left ureteric orifice. Circumcision and correction of the penoscrotal web were performed. The patient had an uneventful recovery and was discharged on the postoperative day 1. Parents were counseled regarding close monitoring for symptoms of urinary tract infection and dysuria. On follow-up, the patient continued to be asymptomatic.

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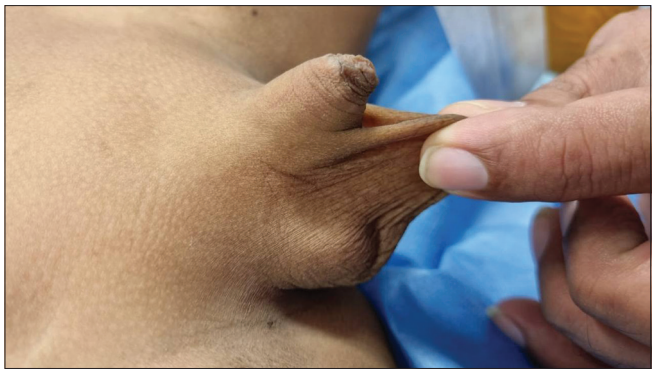

Figure 1: Photograph showing phimosis with balanoposthitis, along with a penoscrotal web and mild dorsal chordee

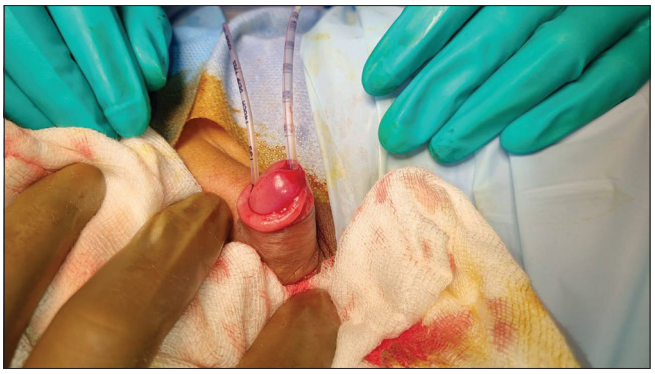

Figure 2: Photograph showing ventral urethra was catheterized with an 8 Fr infant feeding tube and the dorsal urethra cannulated with 6 Fr infant feeding tube

Discussion

Duplication of the urethra refers to a spectrum of rare congenital anomalies characterized by the presence of two urethral channels. With fewer than 300 cases reported in the literature so far, the exact embryologic mechanism for the duplication of the urethra is still not understood.

Some leading theories include:

a. Irregularity in ingrowth of lateral mesoderm of the cloacal membrane leading to epispadic varieties as described by Casselman and Williams[4]
b. Epispadic urethra is also thought to be associated with the exstrophy epispadias complex, with a failure of separation of two primitive layers of the cloacal membrane[5]
c. Transient overactivity of the Mullerian system and failure of normal development of the urorectal septum[6] leading to more ventral duplications
d. Division of the notochord in an earlier phase of embryonic development leading to caudal duplications.[3]

They can also be associated with duplication of bladder, external genitalia, VACTERL (vertebral [V], anal [A], cardiac [C], tracheoesophageal fistula with or without esophageal atresia [TE], renal [R], and limb defects [L]) anomalies, posterior urethral valves, vesicoureteric reflux, ectopic/horseshoe kidney, renal agenesis, and other anorectal malformations.[2-12]

The presentation can be varied with common presenting complaints being: double urinary stream, obstruction, dysuria, recurrent urinary tract infections, incontinence, and dribbling of urine from ectopic urethra. Asymptomatic presentation detected incidentally as described in our case, is also relatively uncommon.

After extensive literature search on platforms including PubMed and Google Scholar, few case reports were found of complete urethral duplication. The diagnosis and management of this entity continue to be a challenge due to the rarity of this anomaly.

We have used the Effman classification system as it is the most comprehensive. It broadly divides urethral duplications into three types [Figure 3]:[3]

- Type I: Blind incomplete urethral duplication (accessory urethra)
  a. Distal opens on the dorsal or ventral surface of the penis but does not communicate with the urethra or bladder
  b. Proximal opens from the urethral channel and ends blindly in the periurethral tissue.
- Type II: Complete patent urethral duplication
  a. Two meatus
    1. Two noncommunicating urethras arising independently from the bladder
    2. The second channel arises from the first and courses independently into a second meatus.
  b. One meatus
    1. Two urethras arise from the bladder or posterior urethra and unite into a common channel distally.
- Type III: Urethral duplication as a component of partial or complete caudal duplication.

Another classification system has been proposed by AbouZeid *et al*., which takes into account coronal and sagittal duplications; however, the Y-type urethroperineal fistulae are excluded from this classification.[8]

Our patient was identified to have Type II A-1 as per Effman classification. Recent case series have identified Type II A-2 to be the most common subtype.[9,10]

Evaluation of the condition for operative intervention is incomplete without identifying the exact anatomy, recognition of the more functional urethra, and investigation for any associated anomalies.[13]

After careful clinical examination, a voiding cystourethrography can be performed if there is a high index of suspicion regarding duplication. Sonography of the kidney and urinary bladder is a noninvasive and easily accessible test that can be done to rule out any other concurrent anomalies like an absent kidney.

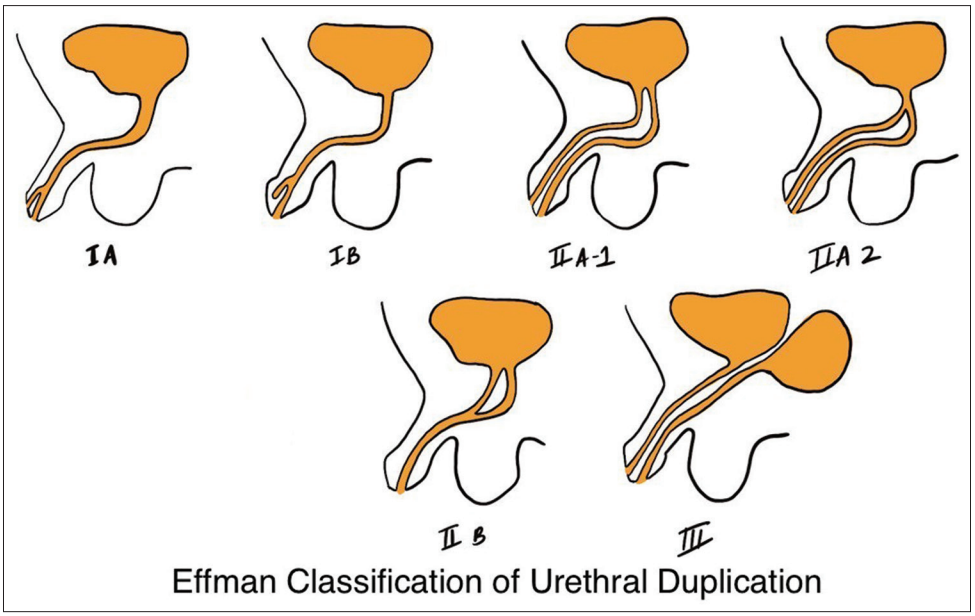

Figure 3: Diagram of Effman classification

Before planning surgical intervention, the more functional urethra must be identified. Voiding studies are of benefit for the same.

Different approaches to operative management have been described depending on the type and presentation of duplication.[14,15] Treatment must aim to preserve continence and renal function and has the best cosmetic outcome. In case of sagittal duplications, the smaller or hypoplastic urethra must be identified and is surgically excised. In most cases, this is the ventral urethra and care must be taken to preserve verumontanum and sphincter during repair. Failure to do so results in incontinence. Complex Y-type fistulae require urethroplasties and staged procedures with buccal mucosal grafts.

It is generally accepted that surgical correction can be avoided if the patient is asymptomatic, as was the case for our patient.[16] The patient was worked up for any associated anomalies and correction for the presenting symptoms was done. A close monitoring strategy was applied and surgical morbidity was kept to a minimum with this approach.

Conclusion

Duplication of the urethra is a rare congenital anomaly, predominantly seen in males. Due to the rarity of the condition, there is no fixed consensus regarding the management of these patients. Asymptomatic complete duplication of urethra like in our patient of Effman Type II A-1 is an even rarer entity. The correction of associated anomalies and proper follow-up is recommended as in our case. Our aim is to report this rare case and to enhance the knowledge by reviewing the already existing scanty literature of this condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Therapeutic Options in Metastatic Renal Cancer

Themistoklis Ch. Bellos[1], Ioannis S. Manolitsis[1], Stamatios N. Katsimperis[1], Ioannis P. Kyriazis[1], Panagiotis A. Angelopoulos[1], Panagiotis N. Neofitou[1], Sotirios G. Kapsalos-Dedes[1], Panagiotis K. Deligiannis[1], Lazaros I. Tzelves[2], Nikolaos A. Kostakopoulos[1], Lazaros C. Lazarou[1], Titos P. Markopoulos[1], Marinos V. Berdempes[1], Alexandros A. Kiriakidis[1], Konstantinos E. Livadas[1], Iraklis C. Mitsogiannis[1], Ioannis M. Varkarakis[1], Athanasios G. Papatsoris[1], Andreas A. Skolarikos[1], Charalampos N. Deliveliotis[1]

Abstract

Background: Renal cancer is the 3rd most common cancer of the urinary tract. It peaks at the age of 64 years and appears more common in men than women. **Methods:** The purpose of this study is to review the potential therapeutic options in metastatic renal cancer. A thorough MEDLINE/PubMed nonsystematic literature review was conducted from 1990 to May of 2023. The terms used for the search were "metastatic" AND "renal cancer" OR "renal cell carcinoma" AND "therapy" OR "treatment" AND "metastasectomy" AND "immunotherapy". **Results:** Metastasectomy is advantageous when the metastatic foci are completely excised. When there is no clinical suspicion of any remaining metastatic disease, there is no need for further systemic therapy. Patients at intermediate risk may initiate neoadjuvant systemic therapy with immune-oncology (IO) and IO or tyrosine kinase inhibitor and IO; once the tumor regresses, metastasectomy is performed. **Conclusion:** In conclusion, there are many modalities for metastatic renal cancer treatment which depend on the prognostic factors of the disease itself.

Keywords: *Immune checkpoint inhibitor, immune-oncology, immunotherapy, metastasectomy, metastatic renal cancer, tyrosine kinase inhibitor*

Introduction

Renal cell carcinoma (RCC) encompasses a diverse range of histological types, with clear cell RCC (ccRCC) being the predominant subtype, accounting for around 70%–75% of all renal tumors. Papillary and chromophobe RCCs account for 10% and 5% of the remaining cases, respectively. A proportion ranging from 4% to 6% of tumors cannot be definitively classified into any distinct RCC subgroups.[1] RCC ranks as the 14th most prevalent form of cancer.[2,3] In the year 2008, there were approximately 274,000 newly reported instances of RCC globally, resulting in 72,000 deaths attributed to kidney cancer. The age-standardized mortality rate for this condition was recorded as 2.2/100,000 individuals. The incidence of RCC has demonstrated an upward trajectory during the past 20 years. However, in more recent times, this pattern has experienced a cessation and a partial reversal. The prevalence of advanced renal tumors has declined in favor of smaller, less advanced tumors, owing to the improved accessibility of ultrasound and computed tomography (CT). This phenomenon results in an improved prognosis and reduced mortality rates.[4]

In the United States, renal cancer has the lowest relative survival rate of all urogenital cancers, at 76%. Nearly one-third of renal malignancies are initially diagnosed with metastatic, and 20%–40% of those that are initially diagnosed as localized progress to metastatic, despite being excised. 12%–15% is the 5-year survival rate for grade 4 metastatic RCC (mRCC).[5] The most common sites of metastasis for RCC are the lungs (45%–60%), followed by the bone metastases (30%), lymph nodes (LNs) and liver metastases (20%), and infrequently the adrenals, brain, and pancreas. A CT examination of the abdominal and thoracic regions is always conducted when staging renal cancer. Nonetheless, if symptoms from the nervous or locomotor systems are present, imaging of those systems should also be performed, as it is when a known metastatic disease is being monitored.[6]

Methods

The purpose of this study is to review the potential therapeutic options in metastatic renal cancer.In this nonsystematic review, an extensive search was conducted on the PubMed and MEDLINE databases,

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covering the period from 1990 to August 2023. The terms used for the search were "metastatic" AND "renal cancer" OR "RCC" AND "therapy" OR "treatment" AND "metastasectomy" AND "immunotherapy". The screening process involved independent evaluation by one author, followed by a thorough reevaluation by two additional authors. Resolution of Disputes facilitated by Fourth Author in the Medical Literature. Animal studies have been excluded from this particular review.

Prognosis

The prognosis of metastatic renal disease is based on the prognostic models of Memorial Sloan Kettering Cancer Centre (MSKCC) and the more recent of International Metastatic Renal Cancer Database Consortium (IMDC), in which the presence of thrombocytosis and neutrophilia replaces an increase in Lactate Dehydrogenase as a prognostic marker.[6] Other prognostic factors include disease-free survival since nephrectomy, tumor characteristics (T stage >3, high grade, sarcomatoid features, LN invasion), and the patient's performance status (Karnofsky score >80 is associated with a favorable prognosis).[7]

There exists a lack of agreement in the delineation of risk groups across the two models. According to available data, around 54.1% of patients belonging to the poor risk category at MSKCC are categorized into the intermediate risk group according to the international mRCC Database Consortium classification. In addition, it has been observed that around 20.2% of patients from the intermediate risk group at MSKCC are classified into the favorable IMDC risk group.[8]

Therapy

Localized therapy, which includes either the primary cancer (cytoreductive nephrectomy (CN), embolism) or the metastases (metastasectomy, radiotherapy, and embolism), and systematic therapy (targeted therapy, immunotherapy, and tyrosine kinase inhibitors [TKI]) comprises the treatment for metastatic renal cancer.

Cytoreductive nephrectomy

CN is indicated in patients with minimal risk and good prognosis based on prognostic models for metastatic renal diseases who do not require systematic therapy, or in patients with intermediate prognosis who initially respond to the systematic therapy. It is also recommended for patients with oligometastatic disease for whom complete resection of metastases is feasible.

CARMENA, a phase III noninferiority randomized controlled trial comparing CN followed by sunitinib to sunitinib alone, demonstrated that sunitinib alone was not inferior to CN followed by sunitinib in terms of overall survival (OS).[9] According to the EORTC SURTIME study, the order in which CN and sunitinib were administered did not affect progression-free survival (PFS) (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.59–1.37, P = 0.569). CN is not recommended for patients with poor PS or low IMDC risk, small primary tumors, large metastatic volume, or a sarcomatoid tumor.[10] CARMENA confirms these findings, and it appears that presurgical VEGFR-targeted therapy followed by CN is advantageous.[11] Immune checkpoint inhibitor (ICI) combination therapy with sunitinib and other Vascular Endothelial Growth Factor (VEGFR)-TKI is now recommended as the first-line treatment for patients with an established primary tumour, with monotherapies reserved for those who cannot tolerate ICI combination therapy or do not have access to these medications. A recent systematic review of the effects of CN revealed an OS benefit for CN in patients with mRCC who do not require immediate pharmacological treatment.[12]

Metastasectomy

When the complete removal of metastatic foci is practicable, metastasectomy can provide significant benefit for cancer-specific survival (CSS).[6,13] Moreover, it has been demonstrated that the initial metastasectomy followed by systematic therapy, i.e. immunotherapy and TKIs improve survival rates for these patients.[14] Compared to other foci, radical lung metastasectomy has a superior prognosis and typically fewer complications. Metastasectomy of tumors in weight-bearing joints or bones, vertebrae with imminent spinal cord compression, or brain tumors should be followed by systemic therapy or radiotherapy, as excision alone is typically insufficient.

In accordance with the European Association of Urology (EAU) guidelines, metastasectomy should be performed when extirpation of metastatic foci is achievable,

as it improves OS, CSS, and can delay the initiation of systemic therapy required for disease control. In contrast, when there is no clinical suspicion of remaining metastatic disease (stage cM0), no systematic adjuvant therapy is recommended following complete metastasectomy. A recent study, Keynote-564, in which adjuvant immunotherapy (Pembrolizumab) was administered to a limited number of patients (n = 58), who were in the cM0 stage after metastasectomy, demonstrated an improvement in disease-free survival. Due to the limited number of participants, however, the EAU guidelines did not change.

Other therapies

Stereotactic radiotherapy is recommended by the EAU guidelines for clinically significant bone and brain metastases, as well as for local disease control and symptom relief, such as pain. Stereotactic radiation has been shown to provide local control for a minimum of 1 year in 84% of patients. When used in combination with surgical treatment, this percentage increases to 94% in patients with brain metastases.[15] Except for radiation therapy, the embolism of metastatic foci, which is indicated before the excision of highly vascularized bony or vertebral metastasis, plays an essential role in the control of the disease. In order to minimize blood loss, this procedure is performed. It could also aid in the treatment of bone metastases due to its analgesic properties.[6]

Systematic therapy

The treatment approach for RCC at the systemic level encompasses the use of several therapeutic agents. These include the combination of bevacizumab with interferon alfa (IFNα), TKIs, serine-threonine kinase inhibitors mammalian target of rapamycin receptor (mTOR), and immunocompetent medicines. The implementation of cytostatic treatment is restricted to a limited number of situations.

Molecular targeted therapy

The investigation into the impact of Von Hippel Lindau protein and heightened angiogenesis on the pathogenesis of RCC has played a crucial role in advancing the treatment of RCC and the emergence of targeted therapeutic approaches.

Vascular endothelial growth factor inhibitors

The use of bevacizumab, a recombinant humanized monoclonal antibody, has been authorized for the treatment of mRCC. The mechanism of action of bevacizumab involves the suppression of vascular endothelial growth factor (VEGF) interaction with its surface receptors on the vascular endothelium, hence impeding angiogenesis. This process effectively hinders the growth of several types of solid tumors, including RCC.

The AVOREN phase III research assessed the effectiveness and safety of combining bevacizumab with IFNα as a first therapy option. This study covered individuals diagnosed with dominant ccRCC. A comparison was made between monotherapy using IFNα-2a and combination therapy using bevacizumab and IFN. The study showed a significant increase in PFS, whereas no impact on OS was observed.[16] The results presented in this investigation align with the conclusions found in the CALGB90206 study.[17] The combination of bevacizumab and IFNα-2a has been granted approval for use in the initial treatment of advanced and mRCC, as per drug registration.

Tyrosine kinase inhibitors

The transmission of the cellular signal relies on the existence of receptor proteins. Upon the stimulation of extracellular molecules, the exposure of surface receptors leads to the activation of secondary messengers through the process of phosphorylation. Excessive activation of tyrosine kinase has the potential to result in unregulated cellular proliferation and the formation of metastatic lesions. TKIs are a class of small molecules that effectively suppress the activity of a secondary messenger pathway. There are seven distinct kinase inhibitors that hold notable significance in the therapeutic management of RCC. These inhibitors include sorafenib, sunitinib, pazopanib, axitinib, tivozanib, lenvatinib, and cabozantinib. From a biological standpoint, these substances exhibit variations in terms of their potency and range of inhibitory effects, which directly correlates with their effectiveness in combating tumors and the likelihood of adverse reactions.

Initial outcomes of sorafenib, a kinase inhibitor, were underwhelming. Research comparing IFNα-2a with sorafenib has indicated that there is no significant disparity in terms of PFS and OS.[18] Nevertheless, the TARGET research, which conducted a comparison between sorafenib and placebo, documented a positive outcome in terms of PFS while observing no impact on OS among patients who exhibited resistance to cytokine treatment. After taking into account the fact that sorafenib was administered following the progression of cancer, a statistically significant improvement in OS was seen.[19] Sorafenib has received approval for the treatment of patients diagnosed with advanced RCC who have experienced treatment failure with past IFNα or interleukin-2 (IL-2) based therapy, or are deemed ineligible for such therapeutic interventions.

Sunitinib has demonstrated enhanced potency as a TKI. A comparative study was conducted to assess the efficacy of sunitinib as a first-line treatment in comparison to IFNα. The results indicated that the group receiving sunitinib had a higher median OS, although the statistical significance of this finding was only marginally significant (P = 0.051). The sunitinib group exhibited a statistically significant increase in median PFS compared to other groups.[20,21] Furthermore, a meta-analysis conducted in 2015 demonstrated that the administration of sunitinib as the initial therapy option resulted in a significant increase in the median PFS

compared to other therapies such as bevacizumab–IFNα, everolimus, sorafenib, and temsirolimus–bevacizumab. There were no significant differences observed in PFS outcomes among the treatment groups receiving sunitinib, axitinib, pazopanib, and tivozanib, as reported in reference.[22]

Currently, sunitinib stands as the sole pharmaceutical agent employed in adjuvant therapy subsequent to severe surgical intervention for patients exhibiting a heightened susceptibility to recurrence. The findings of the S-TRACK trial indicate that the administration of sunitinib leads to a significant increase in the median PFS, with a duration of 6.8 years, as compared to the placebo group, which exhibited a median PFS of 5.6 years. There is a lack of definitive data pertaining to the OS rate.[23] In contrast, the three-arm ASSURE study examined the efficacy of adjuvant therapy with sunitinib or sorafenib compared to a placebo. However, no significant disparities in terms of PFS or OS were seen. The authors did not specify a particular demographic that might derive advantages from this treatment.[24] The authors of the S-TRACK trial provide an explanation for the inconsistencies observed in the results. They attribute these discrepancies to two factors: the central evaluation of CT scans conducted in the S-TRACK investigation and the implementation of more stringent inclusion criteria, which limited the study group to patients with high-risk ccRCC exclusively.[23] The Food and Drug Administration (FDA) granted approval for the use of sunitinib as an adjuvant treatment in adult patients with a high risk of recurring RCC after undergoing nephrectomy, based on the findings of the S-TRACK research. Sunitinib is exclusively authorised for the management of advanced and mRCC in adult individuals within the European region.

Pazopanib represents an additional pharmaceutical agent within the class of TKIs. A Phase III clinical trial was conducted to compare the efficacy of pazopanib with placebo as a first- and second-line treatment following first cytokine therapy. The study findings revealed a significant improvement in PFS associated with the use of pazopanib. In subpopulations that did not receive neoadjuvant therapy, as well as those that were initially treated with cytokines, there were statistically significant differences in PFS (2.8 vs. 11.1 and 4.2 vs. 7.4, respectively).[25] Subsequent investigations comparing the therapeutic outcomes of pazopanib and sunitinib revealed comparable efficacy between the two medications, while also highlighting the enhanced tolerability of pazopanib.[26,27] However, the study did not provide evidence of any benefit in using pazopanib as an adjuvant treatment following radical treatment.[28]

Axitinib, classified as a second-generation TKI, exhibits significantly higher binding affinity to VEGF receptors compared to earlier generations of TKIs. Consequently, it is seen as a viable therapeutic option for RCC patients who have already had prior lines of treatment. A comparative study was conducted to evaluate the efficacy of axitinib in comparison to sorafenib in patients who experienced treatment failure with their initial systemic treatment. The results of the study indicated that axitinib considerably increases the median PFS, while not affecting the OS.

In a separate investigation conducted by Motzer *et al*., a comparison was made between tivozanib and sorafenib as first therapy and subsequent treatment following the failure of the primary treatment. The findings of this trial revealed a significant extension in PFS within the tivozanib group. In contrast, the sorafenib arm exhibited a greater OS, with a median OS of 29.3 months compared to 28.8 months. One of the limitations of this trial was the potential bias in the selection of patients, as those in good health were more likely to get sorafenib initially and, in the event of treatment failure, tivozanib was administered.[29] Hence, tivozanib did not obtain approval in the United States. The European Medical Agency has granted approval for the use of tivozanib as a first-line treatment option for adult patients diagnosed with advanced RCC. Additionally, tivozanib is approved for adult patients who have not previously received VEGFR and mTOR pathway inhibitors and have experienced disease progression after one prior treatment with cytokine therapy for advanced RCC.

Prolonged administration of VEGF receptor inhibitors induces the upregulation of alternative pathways, hence facilitating the advancement of the disease. The comprehension of this mechanism facilitates the advancement of novel TKIs with wider-ranging efficacy. Lenvatinib functions as a TKI, specifically targeting receptors for VEGF and fibroblast growth factor. The study showed that a combination therapy involving lenvatinib and everolimus, a mTOR inhibitor, was more efficacious in treating patients who had experienced progression with VEGF signaling-guided treatment, compared to the use of lenvatinib or everolimus as monotherapy.[30]

Cabozantinib is a pharmaceutical compound that acts as an inhibitor of VEGF, AXL, and MET kinase receptors. The AXL and MET receptors have been found to be correlated with the development of resistance to treatment targeting the signaling pathway of VEGF. A comparative analysis was conducted to evaluate the efficacy of cabozantinib against everolimus as therapy options following the development of resistance to conventional VEGF signaling kinase inhibitors. The study findings revealed that patients receiving cabozantinib experienced a significantly longer median PFS and OS compared to those receiving everolimus.[31] A study was undertaken to evaluate the effectiveness of cabozantinib compared to sunitinib for patients with mRCC who were classified as having poor or intermediate risk. The investigation was motivated by the high efficiency associated with cabozantinib. The study provided evidence of an extended duration of PFS, while there is currently a lack of comprehensive data pertaining

to OS.[32] Cabozantinib has been granted authorization by the FDA and EMA for its use as a first-line treatment in individuals, as well as for patients who have seen disease progression subsequent to prior anti-VEGF therapy.

Threonine-serine kinase inhibitors: Mammalian target of rapamycin recepto

Theonine Serine Kinase Inhibitors (STK) inhibitors refer to a class of pharmaceutical compounds that exert inhibitory effects on mTOR kinase, a crucial regulator of cellular proliferation. The control of cancer growth can be achieved through the inhibition of mTOR activity, which effectively hinders protein translation and subsequently regulates the biological cycle. The disruption of protein synthesis and cellular division occurs when phosphorylation is inhibited and the proteins 4E-BP1 and S6K are activated. Additionally, it has been suggested that the mTOR kinase may have a role in regulating the translation of hypoxia-inducible factor 1 and 2, leading to a reduction in the neoplasm's ability to adapt to hypoxia and a suppression of angiogenesis through the inhibition of VEGF synthesis.[33]

Temsirolimus, an inhibitor of serine/threonine kinases (STK), was the initial therapeutic agent to receive approval for the treatment of RCC. Hudges *et al*. undertook a study to assess the efficacy of temsirolimus in individuals diagnosed with RCC and exhibiting a poor prognosis. The participants were allocated into different groups, each of which received either temsirolimus, IFN-α, or a combination of both. The patients who received temsirolimus had the highest median PFS and OS rates.[34] Temsirolimus was granted approval in the European Union for the initial therapy of patients diagnosed with advanced RCC who exhibit a minimum of three out of six prognostic risk factors, as indicated by the findings of this study.

In contrast, a research investigation comparing the efficacy of everolimus medication to placebo following initial treatment failure with sunitinib, sorafenib, or a combination of both, revealed an extension of PFS and no discernible disparity in OS among patients receiving everolimus.[35] As per the medication approval registry, everolimus has received approval for the treatment of individuals diagnosed with mRCC subsequent to the ineffectiveness of a prior VEGF-targeted therapy.

Immunotherapy

The presence of T cells infiltrating the tumour, along with the occasional instances of spontaneous remission of metastatic disease, indicates that RCC has a high degree of immunogenicity.[36] The aforementioned observation served as the catalyst for the advancement of immunologic therapy. The primary trials that studied the effect of ICIs on mRCC patients are depicted in Table 1.

The utilisation of cytokine-based immunotherapy including IFN-α or IL-2 has demonstrated efficacy as a therapeutic approach for a limited subset of individuals afflicted with mRCC. The treatment with IFN-α is supported by its theoretical foundation, which is rooted in its diverse range of actions. These actions include direct inhibition of cell proliferation and angiogenesis, enhancement of the lytic activity of natural killer lymphocytes, and induction of the expression of various antigens, such as class I HLA antigens, on the surface of cancer cells. Therefore, cytotoxic T lymphocytes identify and eliminate tumour cells. The Medical Research Council conducted a randomised research which found that monotherapy with IFN resulted in a median OS increase of 2.5 months compared to medroxyprogesterone.[37] At present, due to the increased accessibility of more efficacious treatment options, the utilisation of monotherapy including IFN-α is regarded as outdated.

IL-2, a type of cytokine, holds significant prominence as a growth factor for T lymphocytes. The approval of high dosage therapy with IL-2 (HD IL-2) for the treatment of mRCC was based on the findings from seven multicenter studies conducted during phase II, and was granted by the FDA. Based on the latest data, it has been determined that a therapeutic response is achieved by 15% of patients treated with high-dose interleukin-2 (HD IL-2). The median duration of response is 54 months. A study found that a complete remission was observed in 7% of patients, and this remission was sustained for a period ranging from 3 to 131 months, with a median duration of 80 months.[38]

Table 1: Key trials on immune checkpoint inhibitors on metastatic renal cell carcinoma

Trial	Drug combination	Number and percentage of patients treated with primary tumor in place (%)	Number of patients treated with primary tumor in place (ICI combination versus sunitinib)		Subgroup analysis (HR with 95%CIs)	
			ICI combination	Sunitinib	PFS	OS
Checkmate 214	Ipilumab + nivolumab	187/847 (30.1)	84	103	NA	0.63 (0.42–0.94)
Checkmate 9ER	Cabozantinib + nivolumab	196/651 (30.1)	101	95	0.63 (0.43–0.92)	0.79 (0.48–1.29)
Javelin 101	Axitinib + avelumab	179/886 (20.2)	90	89	0.75 (0.48–1.65)	NA
KEYNOTE-426	Axitinib + pembrolizumab	143/861 (16.6)	73	70	0.68 (0.45–1.03)	0.57 (0.36–0.89)
CLEAR	Lenvatinib + pembrolizumab	179/714 (25.1)	97	82	0.38 (0.31–0.48)	0.52 (0.31–0.86)

ICI: Immune checkpoint inhibitor, PFS: Progression-free survival, OS: Overall survival, NA: Not available, HR: Hazard ratio, CIs: Confidence interval

In recent years, there has been a notable advancement in our comprehension of the fundamental regulatory mechanisms governing the activation of immune cells, particularly T-cells. Programmed death receptor 1 (PD-1), a member of the CD28 protein family, is involved in the modulation of T cell activity and significantly contributes to evading immune system regulation. The interaction between the PD-1 receptor and its ligand, PD-L1, on cancer cells has been observed to suppress the proliferation of T lymphocytes, impair their cytotoxic functions, and hinder the production of cytokines. Consequently, this phenomenon results in the programmed cell death of T-cells that are specific to malignancy. The process of lymphocyte differentiation into regulatory T-cells is facilitated, leading to an enhanced ability to resist attack from cytotoxic cells.[39,40]

Nivolumab, an IgG4 antibody that has been humanised and specifically targets the PD-1 receptor, holds considerable importance as a therapeutic agent for the management of mRCC. The method of action involves the inhibition of the PD-1 receptor, hence facilitating the activation and functioning of T-cells. A randomised trial was conducted to compare the efficacy of everolimus and nivolumab in patients with progressive RCC following first or second-line antiangiogenic treatment. The results of the study revealed a higher frequency of therapeutic response (25% vs. 5%) and a reduced risk of mortality in the group receiving nivolumab. The therapeutic efficacy of nivolumab remained consistently high regardless of the expression of PD-L1 in the primary tumour. Furthermore, the incidence of grade 3 or grade 4 adverse events was comparatively lower in the cohort that received nivolumab. The study has shown a notable and consistent enhancement in the average quality of life over a span of 2 years with the administration of nivolumab.[40] According to the findings of this study, the use of nivolumab as a standalone treatment has been authorised in Europe for adult patients with advanced RCC who have already undergone therapy. Further investigation was required to assess the efficacy of nivolumab as a first-line treatment, given the encouraging outcomes of contemporary immunotherapy in patients who experienced progression following kinase inhibitor therapy. A comparative investigation was conducted to assess the efficacy of combined treatment using nivolumab and ipilimumab in patients with mRCC. The study revealed that individuals with intermediate and bad prognoses who received immunotherapy exhibited improved outcomes. Nevertheless, it has been observed that individuals with a favourable prognosis would experience greater advantages from the administration of sunitinib as a form of treatment.[41] Presently, numerous research investigations are underway to assess the efficacy of immunotherapy as adjuvant therapy. Additionally, studies are being conducted to examine the impact of various immunocompetent drugs, such as pembrolizumab, atezolizumab, and avelumab, in the treatment of RCC. Furthermore, investigations are exploring the potential benefits of combining immunocompetent drugs with antiangiogenic drugs. Lastly, the utilisation of immunotherapy in the treatment of patients with non-ccRCC is also being investigated.

Special clinical situations

There are uncertainties regarding the efficacy of systemic treatment in some clinical scenarios. This pertains to individuals with an alternative histological variety, specifically non-ccRCC, which exhibits unique neoplastic characteristics. An additional illustration can be seen in the case of central nervous system metastases, wherein the efficacy of drug penetration is constrained by the brain–blood barrier. Patients diagnosed with non-ccRCC represent a relatively small proportion within the overall population of individuals affected by renal cancer. The scarcity of alternative histological variants poses significant challenges when attempting to perform phase III trials to address this issue. Furthermore, it is worth noting that the prevailing pathological pattern observed in the majority of research investigations is ccRCC. The investigation involving temsirolimus stands as a singular deviation. In the Phase III registration research, it was observed that 20% of the patients exhibited histology that differed from ccRCC. The study provided evidence that individuals diagnosed with non-ccRCC experience more therapeutic advantages from temsirolimus treatment as opposed to IFN. Further information regarding the treatment of these patients is derived from expanded access trials. The results of an extended access trial with sunitinib revealed that a significant proportion of patients diagnosed with non-ccRCC experienced clinical benefit. This benefit was defined as either a therapeutic response or disease stabilisation. Specifically, 68% of the patients enrolled in the experiment achieved this desired outcome. Regardless of the histology, a clinical benefit was observed in 76% of patients with RCC. In contrast, it has been observed that sorafenib has clinical efficacy in 90% of individuals diagnosed with chromophobe RCC and 84% of people diagnosed with papillary RCC. It is not feasible to compare the outcomes of both investigations due to disparities in the chosen end-points.[42,43]

Based on an investigation conducted on a sample size of over 11,000 patients, it has been estimated that brain metastases contribute to around 8% of the improved outcomes observed in mRCC cases.[44] The advancement of novel therapeutic approaches, with the refinement and customization of medical treatments, instills optimism for continued advancements in this field.

Conclusion

In summary, the surgical removal of metastatic foci, known as metastasectomy, is recommended for cases of RCC where complete excision is feasible. This surgery may be followed

by systematic therapy or repeated metastasectomies in instances of clinical disease progression or the reappearance of metastatic foci. Stereotactic radiation is commonly employed for the treatment of bone and cerebral metastases, while embolisation is often utilised for the management of severe bone metastases. The results of the CARMENA and SURTIME studies suggest that patients who are in need of systemic therapy experience positive outcomes when they receive prompt pharmacological intervention. Ongoing randomised trials are currently comparing the outcomes of deferred CN versus no CN when combined with ICIs and ICI combinations. Preliminary findings from trials involving ICI combinations suggest that the respective combinations of immune-oncology (IO) plus IO or TKI plus IO demonstrate a more favourable impact on both the primary tumour and metastatic sites when compared to the administration of sunitinib alone. Based on the outcomes of the CARMENA and SURTIME studies, it may be inferred that patients with mRCC and those belonging to the intermediate- and low-risk groups according to the IMDC classification, who have an intact primary tumour, should be administered IO-based combination therapies as the initial treatment approach. Patients who demonstrate a clinical response to IO based combinations may be eligible for a subsequent clinical trial.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Current Evidence Regarding Adjuvant Treatment Option in Renal Cell Carcinoma

Abstract

Surgical treatment consists of the gold standard approach in patients diagnosed with nonmetastatic renal cell carcinoma (RCC). However, a great proportion of such patients will relapse postoperatively and metastatic disease will develop. In the present study, we present a review of the literature about available data regarding adjuvant treatment options in patients with RCC treated surgically.

Keywords: *Adjuvant therapy, immune checkpoint inhibitors, renal cell carcinoma, tyrosine kinase inhibitors*

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Introduction

Surgical treatment with either radical or partial nephrectomy is currently the gold standard approach in patients diagnosed with localized renal cell carcinoma (RCC).[1] In cases where the disease is characterized as locally advanced, lymph node dissection is justified even though survival benefit is unclear as it provides information regarding staging and may affect postoperative management strategy.[2] Venous involvement is a challenging situation and data are limited but it is widely accepted that patients with venous tumor thrombus should undergo surgical intervention.[3]

As surgical experience grows, even metastatic disease may be treated with nephrectomy along with metastasectomy provided that all metastatic sites can be removed surgically.[4]

Unfortunately, despite surgical treatment, 20%–30% of patients will develop local recurrence or metastatic disease with the majority being diagnosed within 5 years after surgery.[5] Several anatomical, clinical, and molecular factors incorporated in recurrence or progression modes have been proposed to estimate individual risk.[6] In general, tumor size, nodal involvement, sarcomatoid characteristics on the pathology report, and tumor grade are considered to be the most important factors regarding prognosis.[7] Nevertheless, the question remains whether some groups of patients will benefit from any adjuvant treatment to maximize oncological results after surgery. The aim of this study is to present up-to-date data regarding adjuvant treatment options in patients with RCC treated surgically.

Tyrosine Kinase Inhibitors

Vascular endothelial growth factor receptor targeting tyrosine kinase inhibitors (TKIs) have changed the landscape in metastatic disease management in the pro-immunotherapy era by improving prognosis and are currently used in combination regimens containing one TKI and one immune checkpoint inhibitor (ICI).[8] As a result, several TKIs after proving their benefit on the metastatic status were also tested in the adjuvant setting.

ASSURE Trial

In a double-blind placebo-controlled trial, patients diagnosed with nonmetastatic RCC were randomized to receive sunitinib, sorafenib, or placebo in the adjuvant setting. All patients included were diagnosed with high-grade T1b stage disease or higher. The majority of patients were treated with radical nephrectomy but a small percentage of patients underwent partial nephrectomy was included. Patients with nonclear cell carcinoma were also included. In terms of results, disease-free survival (DFS) was not improved by

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either sunitinib or sorafenib compared with the placebo at the cost of more severe adverse events (Grade 3 or higher) and 5 treatment-related deaths. Discontinuation rates were also high and toxicity issues remained despite the dose reduction.[9]

Final results were published in 2017 supporting that neither sunitinib nor sorafenib proved to be beneficial in the adjuvant setting. No statistical significant difference was noted in DFS or overall survival and authors supported against any adjuvant treatment.[10]

PROTECT Study

This phase III trial evaluated the efficacy and safety of pazopanib versus placebo in patients with locally advanced RCC including a total of 1538 patients. Most patients had undergone radical nephrectomy apart from a small percentage treated with partial nephrectomy. Postoperatively, patients with resected pT2 (high grade) or ≥ pT3, including N1, and clear cell RCC were randomly assigned to pazopanib or placebo for 1 year. Treatment dose of pazopanib started at 800 mg but was subsequently reduced to 600 mg due to toxicity issues. DFS results of pazopanib 600 mg showed no benefit compared with placebo.[11] Motzer *et al*. published the final results in 2021 concluding that adjuvant treatment with pazopanib did not improve overall survival in patients with localized or locally advanced RCC and thus it should not be offered as treatment option.[12]

S-TRAC Trial

In the S-TRAC trial, the role of sunitinib was evaluated compared with placebo as adjuvant treatment in 615 patients diagnosed with locoregional RCC but at high risk for relapse after surgery.

Patients should present clear cell RCC of T3 or T4 stage with or without lymph node involvement before nephrectomy. Sunitinib was administered at 50 mg/day on 4 weeks on followed by 2 weeks off protocol for a total of 1 year with the permission of dose reduction to 37.5 mg according to toxicity reports. DFS was 6.8 years in the sunitinib arm compared with 5.6 years in the placebo (P = 0.03). Although overall survival benefit was not proved due to immature results, DFS benefit was promising but at a cost of more Grade 3 or 4 adverse events in the sunitinib group.[13] Based on the aforementioned results and despite the absence of overall survival results, the Food and Drug Administration (FDA) approves in 2017 the use of sunitinib as adjuvant treatment in patients at high risk of relapse. In 2018, Motzer *et al*. published the updated results including subgroup analyses and overall survival data. DFS benefit was noted in subgroups but median overall survival results remained immature although no trend in favor of sunitinib was noted.[14]

ATLAS Trial

Axitinib was compared with placebo in the adjuvant setting in the ATLAS trial phase III trial.

All patients underwent radical nephrectomy and presented pT2 stage or higher with or without lymph node involvement regardless of Fuhrman grade. Patients were randomized either to receive axitinib 5 mg daily or placebo for a period not <1 year and no more than 3 years. The trial was stopped due to futility at a preplanned interim analysis at 203 DFS events. No statistical difference was noted in oncologic results apart from higher rates of Grade 3 and 4 adverse events in the axitinib group.[15]

SORCE Trial

Sorafenib efficacy was also evaluated in a three-arm trial including patients characterized as intermediate or high risk regarding the risk of relapse. The trial included not only patients with clear cell histology but with other histologic types as well. A major disadvantage of the SORCE trial is that more than 50% of participants stopped treatment at 1 year. Furthermore, no benefit in DFS or overall survival was proven and authors recommended in favor of active surveillance rather than the use of sorafenib as adjuvant treatment.[16]

Immune Checkpoint Inhibitors

Immunotherapy is nowadays part of the backbone treatment in advanced RCC. Since the proved benefit in the metastatic setting, ICIs are investigated in other settings such as the adjuvant with promising results.

KEYNOTE-564

Pembrolizumab was compared with placebo in a double-blind phase III trial in patients who underwent surgery for clear cell RCC characterized as high risk for relapse. Criteria for high-risk definition were T2 stage plus grade 4 or sarcomatoid differentiation, T3 stage or higher, regional lymph node involvement or M1 disease, followed by complete metastasectomy no more than 1 year postnephrectomy. Pembrolizumab was administered at 200 mg once every 3 weeks in a 17 cycles schedule. After 24 months of follow-up, DFS rate was 77% in the pembrolizumab arm and 68% in the placebo (P = 0.002). Moreover, a trend in favor of pembrolizumab in terms of overall survival but not at a statistical significant level. In terms of safety, Grade 3 or higher adverse events were more frequent in the pembrolizumab arm. In total, 32% of patients who received pembrolizumab reported Grade 3 or higher adverse events compared with 18% among those who received placebo.

Furthermore, no decline in quality of life was noted due to treatment.[17] Based on the aforementioned results and despite the lack of overall survival data, pembrolizumab

was recommended as an adjuvant treatment option in patients at high risk for relapse.[18]

IMmotion010 Trial

Pal *et al*. published their results regarding the efficacy of atezolizumab in patients at high risk for recurrence after nephrectomy or even successful metastasectomy. Atezolizumab was compared with placebo with DFS being the primary endpoint. Unfortunately, no benefit was proven in favor of atezolizumab regarding both primary and secondary endpoints.[19]

CheckMate 914 Trial

CheckMate 914 is currently an unpublished trial but in recently and abstract was presented. The primary endpoint of the trial includes DFS per blinded independent central review while secondary endpoints include overall survival and safety. One group of patients received treatment with nivolumab plus ipilimumab or placebo. Another group received only nivolumab, nivolumab plus ipilimumab, or placebo. Yet the primary outcome was not reached and final results are mandatory to draw conclusions.[20]

Discussion

Surgical treatment of locoregional RCC may be insufficient to prevent future recurrence or metastasis in high-risk patients. Thus, it is of outmost importance to apply the best adjuvant treatment available not only to prolong the time to recurrence or metastasis but to prolong overall survival as well. First of all, we must well describe patients who are considered to be at high risk. Several factors are used but clinical trials present heterogeneity in the treated populations.[21] Another issue to be addressed is whether trials regarding adjuvant treatment should include patients who underwent partial nephrectomy even though. In such cases, patients are included, data about positive surgical margins should be taken into account.[22] Undeniably, future research and innovative scientific protocols should be applied. TKIs were the first to be tested in the adjuvant setting. We currently have data from four randomized placebo-controlled studies with only S-TRAC presenting positive results in terms of DFS in high-risk patients treated with sunitinib but at a high cost of adverse events.[13] FDA approval was granted, but probably, it was due to the lack of other alternatives. In clinical practice, sunitinib was not widely used probably due to the safety profile, the initial lack of overall survival data, and the negative results presented in the ASSURE trial.[10] In a recent meta-analysis including the aforementioned trials, a benefit was noted in DFS, especially in high-risk patients, under TKIs treatment but that did not translate into an overall survival benefit. Furthermore, toxicity still remains an important issue.[23]

Immunotherapy using checkpoint inhibitors is a game changer in advanced RCC and is currently investigated in the adjuvant setting. Results from KEYNOTE-564 are promising as far as it concerns DFS. Of course, overall survival data are mandatory to draw strong conclusions.

Although it is not possible to make a head-to-head comparison based on the available data, a benefit of pembrolizumab seems to be the safety profile compared with sunitinib. Pembrolizumab seems to be more well tolerated than TKIs and grade 3 or higher adverse events are encountered less frequently.[17] A major difference in the KEYNOTE-564 is that it included M1 patients who had their metastatic lesions removed successfully no more than 1 year after nephrectomy. It is possible that the positive results regarding DFS were driven from the M1 no evidence of disease (NED) population or from patients presenting with positive lymph nodes.[24]

Conclusion

As data emerge regarding the use of immunotherapy as adjuvant treatment in high risk for relapse after surgery RCC patients, pembrolizumab is currently the only treatment option presenting improved DFS at an acceptable safety profile. As ongoing trials will confirm or not the advantages of immunotherapy, European Medicines Agency and FDA have approved the use of pembrolizumab but patients should be informed about possible toxicity, the possibility of overtreatment, and immature data regarding overall survival.

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Conflicts of interest

There are no conflicts of interest.

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Subcutaneous Emphysema after Transurethral Resection of Bladder Tumor: A Rare Case Report and Review of the Literature

Abstract

Transurethral resection of bladder tumors (TUR-BT) comprises the gold standard surgical approach for the management of the majority of bladder cancer cases, both for the diagnosis and treatment of these cases. Patients subjected to TUR-BT may present with various complications, such as gross hematuria, urinary infection, and postsurgical pain. The incidence of subcutaneous emphysema after TUR-BT is extremely rare and urologists should be aware of this extremely rare complication.

Keywords: *Bladder cancer, bladder perforation, subcutaneous emphysema, transurethral resection, transurethral resection of bladder tumors*

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Introduction

Transurethral resection of bladder tumors (TUR-BT) comprises the gold standard surgical approach for the management of the majority of bladder cancer cases.[1] Pain, infection, blood loss, and bladder perforation constitute the most commonly reported complications occurred after TUR-BT.[2] Although pneumomediastinum and subcutaneous emphysema have been described as the complications of colon or rectal cancer surgeries, these clinical manifestations are rarely reported after bladder perforation.[3,4] Herein, we present the case of a 70-year-old patient that developed subcutaneous emphysema due to bladder ruptures after TUR-BT. To our knowledge, this is the second case report reported in the literature concerning the development of pneumomediastinum after transurethral bladder surgery. The aim of this article is to illustrate this infrequent clinical scenario and to highlight its diagnosis and optimal management.

Case Report

A 70-year-old male was admitted to the urologic emergency department due to severe gross hematuria. He admitted recurrent episodes of hematuria within 1 year that underwent only conservative therapy. His medical history included an occurrence of acute myocardial ischemia with stent placement 2 years ago, atrial fibrillation and hyperlipidemia. His medical treatment consisted of Apixaban and Rosuvastatin. Of note, there was no history of prior surgery, recent travel, or sexual activity. At his admission, blood pressure was 170/95, heart rate at 95 bpm, and O_2 saturation at 97%, while his blood work showed white blood cells: 10.160, hemoglobin: 8.6, hematocrit: 26.3, platelets: 294.000, creatine: 1.6 mg/dL, and C-reactive protein: 16.8 mg/L. Chest X-ray findings were found within the normal limits and preoperative electrocardiography (ECG) showed a normal sinus rhythm. Finally, a suprapubic ultrasonography was performed that showed the development of bladder cancer that filled the whole urinary bladder.

During his hospitalization, routine monitoring was performed including noninvasive blood pressure measurement, ECG, pulse oximetry, and body temperature and he underwent massive bladder irrigation with normal saline. Hematuria was firstly managed conservatively, with several transfusions of blood and frozen plasmas.

During the 2nd day of hospitalization, after cessation of the anticoagulant medication, the surgical team decided to manage his gross hematuria through transurethral hemostasis with spinal anesthesia. TUR-BT was then initiated, using a 0.9% normal saline lifted 50 cm above patient's level

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and 300 mL of blood clots were removed by an Elik and Alexander evacuator. The cutting power was adjusted at 900Watt and a TUR loop was used during the procedure. A mass located in the left wall of urinary bladder was found and subtotal resection of the mass was performed. Due to increased blood loss, great amount of blood clots and low visibility of surgical field, the surgery was urgently ceased and no additional effort for mass resection was performed. The surgeon managed to control the blood loss through hemostasis, while no bladder perforation was noticed during the procedure. A Foley catheter of 22 French was placed and bladder irrigation with normal saline was initiated. The patient returned to the bench side with routine monitoring and remained stable, without need for further transfusions.

Interestingly, on the postoperative day 1, the patient felt discomfort and had dyspnea, with a decline of SpO_2 at 94%. Physical examination showed a crackling feeling of right hemithorax, significant of subcutaneous emphysema. An urgent computed tomography (CT) scan of the thorax, abdomen, and pelvis was performed, discovering small amount of air collection into the bladder, abdominal cavity along with extensive subcutaneous emphysema of the right chest wall and sternum. CT images are presented in Figure 1.

After suggestion of thoracic surgeons, a conservative treatment was decided. The patient remained in the urology department for close monitoring. He remained hemodynamically stable during his hospitalization. Subcutaneous emphysema was gradually disappeared and Foley catheter was removed on 10 postoperative days. The patient was scheduled for a re-TUR and was discharged from the hospital.

Discussion

Although TUR-BT constitutes a common and safe urological surgical procedure, it can be accompanied with various complications, including bleeding and bladder perforation.[2] A vast majority of risk factors have been suspected for the incidence of bladder perforation, such as increased tumor size, multiple bladder resections, and muscle invasive tumor.[5] Furthermore, location of tumor into the posterior wall, increased patient age, and history of bladder treatment comprise additional risk factors.[5] Clinical manifestations related with bladder perforation usually include acute abdomen, lower abdominal pain, and abdominal distention.[6,7] Pneumoperitoneum, pneumomediastinum, or subcutaneous emphysema are rare complications usually occurred after colorectal surgical procedures, whereas the presence of these clinical manifestations after transurethral surgeries remain extremely rare.[3] Of note, bladder ruptures diagnosed at later stages can be life-threatening and thus, high suspicion of physician plays a critical role in the efficient diagnosis and optimal management of these patients.

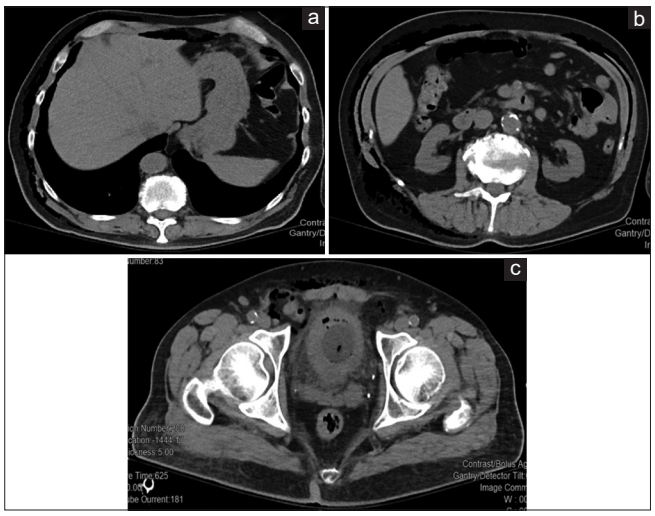

Figure 1: (a) Subcutaneous emphysema in the left hemithorax and behind sternum. (b) Subcutaneous emphysema and intraperitoneal air after bladder rupture. (c) Air inside urinary bladder and intraperitoneal air after bladder rupture

Concerning urological perspective, bladder perforation can be classified as either extraperitoneal or intraperitoneal.[8] Bladder ruptures in the intraperitoneal cavity comprises a life-threatening situation, since it can be complicated by absorption of irrigating fluids resulting to hypovolemia, hypotension and acute renal impairment.[6,9] On the contrary, extraperitoneal perforation constitutes a more frequent clinical manifestation that is related with less severe symptoms.[10] In our case report, both intra and extra-peritoneal perforation of the bladder concurrently occurred. Optimal management of these cases consists of careful evaluation of patient's clinical condition along with constant patient monitoring. According to the literature search, only two cases of subcutaneous emphysema after TUR of prostate and one case after TUR-BT have been reported. Patient characteristics and treatment of these cases are presented in Table 1. In all published cases, surgical procedure was urgently ceased and the patient was transferred to intensive care unit for careful supervision. However, according to our experience, if the patient remains hemodynamically stable, these harmful situations can be managed in clinic's room. Finally, conservative management consisting of careful monitoring and patient support comprise the mainstay of treatment.

The exact pathophysiologic mechanism that permits the development of subcutaneous emphysema after bladder ruptures has not been delineated yet. During TUR-BT, air can be entered into the bladder through various ways. Cystoscope insertion, irrigation tube, instrument manipulation, evacuator usage, and usage of diathermy like bipolar energy are able to induce gas into the bladder.[8] The majority of surgeons suggest that microperforations of bladder allows invasion of air into pelvic retroperitoneum behind the crus and aortic hiatus and later, into the caval foramen of the diaphragm and mediastinum.[8] Another possible mechanism suggests insertion of gas from retroperitoneum to subcutaneous tissues through fascial

Table 1: Published case reports of patients with subcutaneous emphysema after bladder perforation

Author	Age (years)	Surgery	Symptoms	Anatomical area	Treatment
Bagcioglu *et al*.[11]	70	TUR-P	Crackling feeling	Chest wall, neck, face	Conservative
Kim *et al*.[8]	74	TUR-P	Crackling feeling Tense and distended abdomen	Chest wall, neck	Conservative
Cancian *et al*.[12]	85	TUR-BT	NA	Chest wall	Conservative

TUR-BT: Transurethral resection of bladder tumors, TUR-P: Transurethral resection of prostate, NA: No access

planes.[13,14] Finally, an anatomical variation such as opening defect or abdominal hiatum could aid air passage into the mediastinum.[8]

Conclusion

Although subcutaneous emphysema is an extremely rare complication of transurethral resections, the surgeons should be aware of this clinical manifestation and examine the abdomen, chest wall and neck, especially in difficult and prolonged surgical procedures. The presence of any clinical sign of this situation should lead to urgent termination of surgery and close monitoring of patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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