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Bipolar en bloc tumor resection *versus* standard monopolar TURBT – which is the best way to go in non-invasive bladder cancer?

GEORGIANA XENIA BĂLAN[1,2], PETRIŞOR AURELIAN GEAVLETE[1,2], DRAGOŞ ADRIAN GEORGESCU[1,2], COSMIN VICTOR ENE[1,2], CĂTĂLIN ANDREI BULAI[1,2], MARIA ALEXANDRA PĂUNESCU[3], ANDREI NICULAE[2,4], ILEANA PERIDE[2,4], IOAN LASCĂR[5,6], TIBERIU PAUL NEAGU[5,6], BOGDAN FLORIN GEAVLETE[1,2]

[1] *Department of Urology, "St. John" Emergency Clinical Hospital, Bucharest, Romania*

[2] *Clinical Department No. 3, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[3] *Department of Pathology, "St. John" Emergency Clinical Hospital, Bucharest, Romania*

[4] *Department of Nephrology and Dialysis, "St. John" Emergency Clinical Hospital, Bucharest, Romania*

[5] *Department of Plastic Surgery and Reconstructive Microsurgery, Emergency Clinical Hospital of Bucharest, Romania*

[6] *Clinical Department No. 11, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Abstract

The aim of the study was to observe similarities and differences regarding surgical safety and prognosis between en bloc bipolar resection and monopolar transurethral resection of bladder tumors (TURBTs) in medium size papillary non-muscle invasive bladder tumors (NMIBTs). A total of 90 patients with papillary bladder tumors presenting a diameter between 1 and 3 cm were equally divided and alternatively assigned for en bloc bipolar ablation (the study group) and conventional TURBT (the control group). During one year, every three months, the follow-up was performed and the protocol included urinary cytology and cystoscopy. Similar mean patients' age and tumor diameter were determined in both groups. In the study group, it was noticed an important reduced rate of obturator nerve reflex adverse event that caused bladder wall perforation. In addition, comparing the results between the two groups, the following aspects were observed in the study arm: decreased mean operation time (13.4 *versus* 19.7 minutes), hemoglobin level drop (0.28 *versus* 0.76 g/dL), catheterization period (1.9 *versus* 2.8 days) and hospital stay (2.3 *versus* 3.1 days). A total of 41 and respectively 40 patients completed the 12 months follow-up protocol. After one year, the en bloc group presented a significantly lower recurrence rate, superior surgical safety, decreased perioperative morbidity and faster recovery. Therefore, the en bloc surgery approach presented a better oncological prognosis due to the reduced heterotopic NMIBT recurrences up to one year.

Keywords: en bloc resection, TURBT, non-muscle invasive bladder tumors, recurrence rate.

Introduction

Bladder cancer is one of the most common malignancies of the urinary tract and the ninth most frequently encountered in the world [1], complicated by preexisting chronic pathologies, such as diabetes mellitus [2, 3] chronic renal impairment [4], cardiovascular pathologies [5, 6], presenting also a difficult anesthetic management [7]. Due to its high frequency in male patients, bladder cancer can lead to complications related to prostate function [8]. Despite the continuous advances in modern urology, little progress was achieved regarding the proportion of recurrent bladder urothelial carcinomas [9], due to the presence of chronic kidney disease in many patients, pathology associated with severe complications and a median survival at this point between 8–10 months [10, 11]. Bone metastasis can lead to bone demineralization and fragility fractures which require modern, less invasive stabilization methods, trying not to further aggravate the patient condition, being so a constant challenge for the surgeon [12]. Peritoneum metastasis can complicate the management of patient with chronic renal insufficiency, which requires long-term renal replacement therapy [13]. Bladder cancer can primary present with atypical manifestation like pain in the foot or hand, being the consequences of so-called acrometastases, which requires a meticulous differential diagnosis with others malignant or non-malignant disease with similar clinical presentation [14]. Therefore, white light cystoscopy and monopolar transurethral resection of bladder tumor (TURBT) continue to represent the gold-standard diagnostic and treatment in non-muscle invasive bladder tumors (NMIBTs) according to the 2018 *European Association of Urology* Guideline [15, 16].

Bipolar TURBT has already been confirmed by numerous studies as enjoying the advantages of reduced overall perioperative morbidity in general and decreased hemorrhagic risks in particular when compared to the classical monopolar approach, even more so when cases of associated conditions are involved [17–20].

As far as the actual tumor ablation technique is concerned, en bloc resection is consecrated as the beast mean of removing superficial lesions smaller than 1 cm while a staged, layer-by-layer resection is generally acknowledged as the most suitable way of removing tumors larger in size than this threshold [21, 22]. Naturally, the idea of going through the tumor formation with the

resection loop and gradually detaching fragments from it raised questions concerning tumor cells spreading and their bladder mucosa seeding [23]. Although studies in this area of interest remain rather scarce, the respective phenomenon may also constitute at least part of the cause for the still unacceptably elevated NMIBT recurrence rate [24].

Therefore, the question emerged as to the possibility of applying the en bloc resection principle to tumor formations larger than 1 cm [19, 22]. Technically speaking, while taking into account the caliber of the standard resectoscope and the diameter of the human urethra, it was postulated that the en bloc approach may be performed in lesions up to 3 cm in size [22]. Furthermore, the bipolar electrosurgical approach was presumed to provide additional technical feasibility to this alternative treatment modality [22]. Last but not least, the capacity of the en bloc resection to provide a dependable tumor staging clearly represents the ultimate test with regard to the oncological reliability of the procedure [25]. On the other hand, it is obvious that more research regarding recurrence rates is deemed necessary by current literature recently becoming available [26].

The aim of the study was to evaluate the efficiency of en bloc resection by comparison to conventional TURBT in terms of perioperative safety and efficiency features, quality of histopathological analysis in light of the obtained specimens and medium term oncological outcomes.

Patients, Materials and Methods

The study was intended to assess in a prospective manner the bipolar en bloc bladder tumor ablation through a clinical comparison to conventional monopolar resection in patients with medium size superficial bladder lesions. Therefore, between January 2014 and January 2018, a total of 90 patients with papillary bladder tumors between 1 and 3 cm in diameter were equally divided and alternatively assigned for en bloc bipolar ablation and conventional TURBT. The inclusion criteria were similar for all patients of both study arms, while the patients' alternative and equal repartition for the two types of endoscopic approaches was based on and following completion of an informed consent. All patients were diagnosed before surgery by abdominal ultrasound, contrast computed tomography (CT) and flexible cystoscopy as meeting the respective criteria. Furthermore, in light of the pathological analysis subsequent to each procedure, solely non-muscle invasive cases were included in the trial. The exclusion criteria consisted of solid sessile tumors, lesions located in the bladder neck area and tumors involving the ureteral orifice. Following the most recent tendencies of the available literature, technically problematic cases, such as those involving lesions larger than 3 cm in diameter (thus making it difficult to perform the transurethral retrieval) and tumors located in the bladder neck area were avoided as part of the patient' selection process.

As far as the surgical technique was concerned, in half of the cases, en bloc bipolar tumor resection using the hemispherical shape plasma-button electrode and saline irrigation fluid was performed in the study arm. The malignant formation was gradually pushed up and separated from the bladder wall (Figure 1). For this purpose, both the bipolar plasma vaporization and the mechanical detachment using the "button" shape electrode were performed. Given the novelty of this recently introduced type of procedure, it has been considered that only by taking specimens from the tumor bed implantation area using the standard semicircular resection loop, there can be reliably confirmed the accuracy of the malignant tissue ablation process by en bloc resection. Tumor bed plasma-button coagulation constituted the last stage of the procedure. The final aspect of the bladder wall revealed the clean muscular fibers of the detrusor layer, free of malignant tissue, irregularities or debris (Figure 2). The follow-up protocol consisted in abdominal ultrasound, urinary cytology and standard cystoscopy, performed every three months for a period of one year. In accordance with the *European Organisation for Research and Treatment of Cancer* (EORTC) risk recurrence and progression classification tables, chemotherapeutic (Epirubicin) and immunotherapy [bacillus Calmette–Guérin (BCG)] intravesical instillations were applied. Only patients that completed all the periodical check-ups were maintained in the study.

Results

The en bloc and monopolar TURBT series were characterized by similar preoperative parameters including the mean patients' age (64.7 *versus* 66.1 years), tumor diameter (1.82 *versus* 1.69 cm) as well as multiplicity (solitary lesions – 37.8% *versus* 42.2%; multiple tumors – 62.2% *versus* 57.8%) (Table 1).

Table 1 – *Preoperative parameters*

	En bloc resection (*n*=45)	**Monopolar TURBT (*n*=45)**	***p*-value**
Mean patients' age [years]	64.7	66.1	NS[a]
Mean tumor diameter [cm]	1.82	1.69	NS[a]
Solitary lesions	37.8%	42.2%	NS[b]
Multiple tumors	62.2%	57.8%	NS[b]

TURBT: Transurethral resection of bladder tumor; NS: Not significant; [a]Analysis of variance (ANOVA) test; [b]χ^2 (*Chi*-square) test.

While drawing a parallel between the two types of procedure from the point of view of the actual tumor ablation modality, it must be mentioned that, during en bloc resection, tumor detachment was started at the inferior margin of the lesion around the six o'clock position with a deep incision using the sharp edge of the "mushroom" shape electrode, until reaching the muscular layer of the bladder wall (Figure 3). At the end of the intervention, the tumor base bipolar single-wire loop biopsy was applied in order to certify the complete tumor tissue removal using this new technique and to secure the correct tumor staging (Figure 4). In the control arm, classical monopolar TURBT using the conventional semi-circular resection loop was exclusively applied, also finalized by taking separate tumor bed center and margins' biopsies.

From the perspective of surgical features, a significantly reduced rate of obturator nerve reflex adverse events (4.4% *versus* 11.1%) was described in the en bloc series. Moreover, significantly decreased mean operation

time (13.4 *versus* 19.7 minutes), hemoglobin level drop (0.28 *versus* 0.76 g/dL), catheterization period (1.9 *versus* 2.8 days) and hospital stay (2.3 *versus* 3.1 days) were emphasized in the en bloc study group when compared to the classical staged resection.

In light of the pathological analysis analyzing the depth of tumor invasion in the detrusor layer of the bladder wall, similar proportions of pTa (53.3% *versus* 51.1%) and pT1 (46.7% *versus* 48.9%) tumors were revealed among patients of the two study arms (Table 2).

Table 2 – *Perioperative features*

	En bloc resection (*n*=45)	Monopolar TURBT (*n*=45)	*p*-value
Obturator nerve reflex events	4.4%	11.1%	<0.05[b]
Mean operation time [minutes]	13.4	19.7	<0.05[a]
Hemoglobin level drop [g/dL]	0.28	0.76	<0.05[a]
Catheterization period [days]	1.9	2.8	<0.05[a]
Hospital stay [days]	2.3	3.1	<0.05[a]
Pathological results			
pTa	53.3%	51.1%	NS[b]
pT1	46.7%	48.9%	NS[b]

TURBT: Transurethral resection of bladder tumor; NS: Not significant; [a]Analysis of variance (ANOVA) test; [b]χ^2 (*Chi*-square) test.

Most importantly, regarding the evidence-based quality of resection specimens, the detrusor muscular layer was obtained for all tumor formations (removed by either en bloc ablation or standard monopolar TURBT), thus leading to a reliable detection of tumor invasion in all cases (Figures 5 and 6). The similar histopathological profile described by analyzing the specimens obtained using either type of resection was further completed in light of Figures 5 and 6 by the presence of the muscularis propria sheath, without tumor infiltration and with resembling mild or moderate cauterization artifacts. Also, the tumor bed biopsies confirmed the presence of detrusor specific muscle fibers relieved from malignant tissue for the two series, thus certifying the complete tumor ablation achieved by both bipolar en bloc detachment and classical single-wire monopolar loop resection (Figures 7 and 8). Variability among the obtained specimens remains rather wide and at least a non-inferiority perspective may be outlined concerning en bloc resection, while drawing a parallel to monopolar TURBT. For example, subsequent to en bloc resection (Figure 7), the specimen had a well-represented muscular layer in terms of histological aspect, with minimal cauterization artifacts, while conventional TURBT produced severe cauterization artifacts in the tumor layer, making the tumor depth evaluation more difficult (Figure 8).

While referring to the follow-up part of the trial, a total of 41 and respectively 40 patients completed the entire 12 months' protocol. A substantially lower recurrence rate was found in the en bloc group during the summarized one year' check-up (17.1% *versus* 27.5%). While the proportion of same site recurrences remained similar in the two groups (4.9% *versus* 7.5%), en bloc plasma-button resection patients benefited from a significantly decreased rate of heterotopic recurrent lesions (12.2% *versus* 20%) (Table 3).

Table 3 – *Twelve months' follow-up parameters*

	En bloc resection (*n*=41)	Monopolar TURBT (*n*=40)	*p*-value
Recurrence rates	17.1%	27.5%	<0.05[a]
Same site' recurrences	4.9%	7.5%	NS[a]
Heterotopic recurrent lesions	12.2%	20%	<0.05[a]

TURBT: Transurethral resection of bladder tumor; NS: Not significant; [a]χ^2 (*Chi*-square) test.

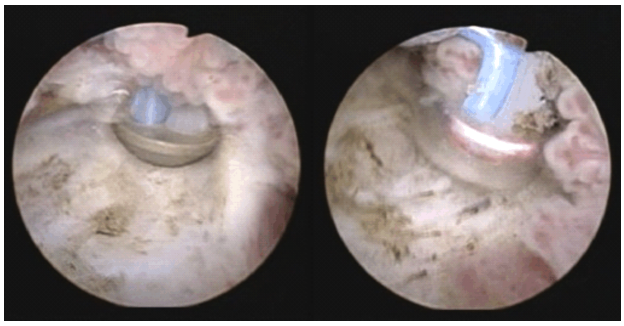

Figure 1 – *Tumor formation gradually pushed up and separated from the bladder wall.*

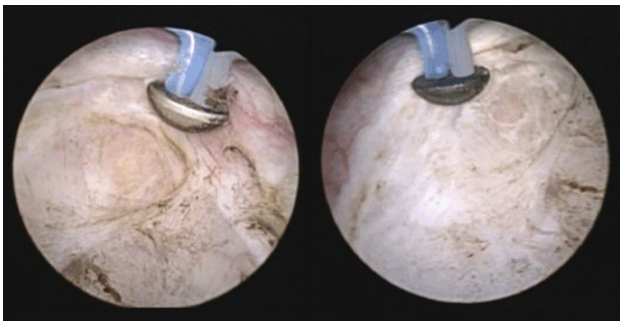

Figure 2 – *Tumor bed final aspect – clean muscular fibers of the detrusor layer, free.*

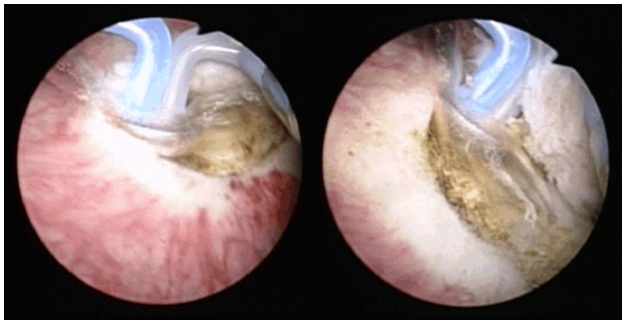

Figure 3 – *Initial tumor detachment – deep incision with the sharp edge of the plasma-button electrode.*

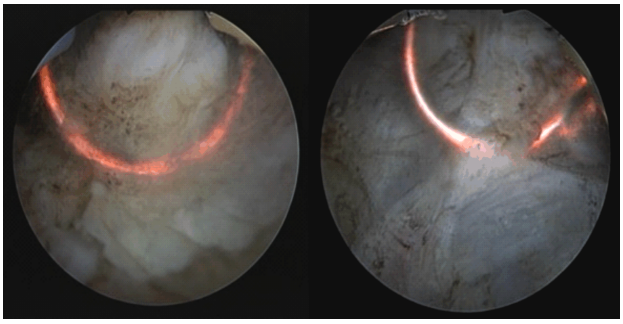

Figure 4 – *Tumor base bipolar single-wire loop resection biopsy.*

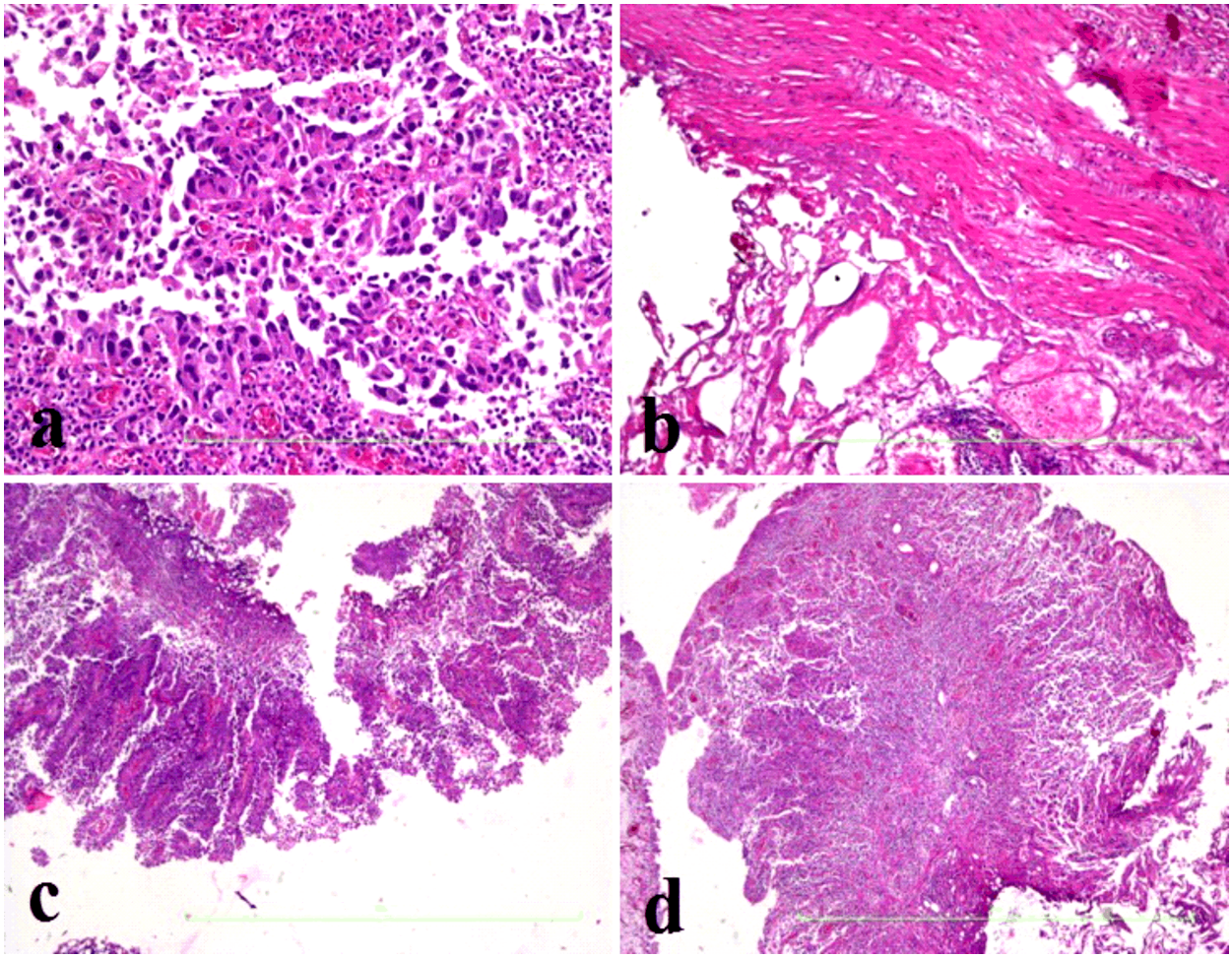

Figure 5 – ***pT1G3 en bloc plasma-button bipolar resection: (a) G3 urothelial carcinoma invasive into the lamina propria – pT1 tumor with high grade nuclear pleomorphism; (b) Lamina propria and muscularis propria from the tumor bed without invasion; (c and d) Papillary high-grade urothelial carcinoma invasive into the lamina propria – pT1G3. HE staining: (a) ×200; (b) ×400; (c and d) ×40.***

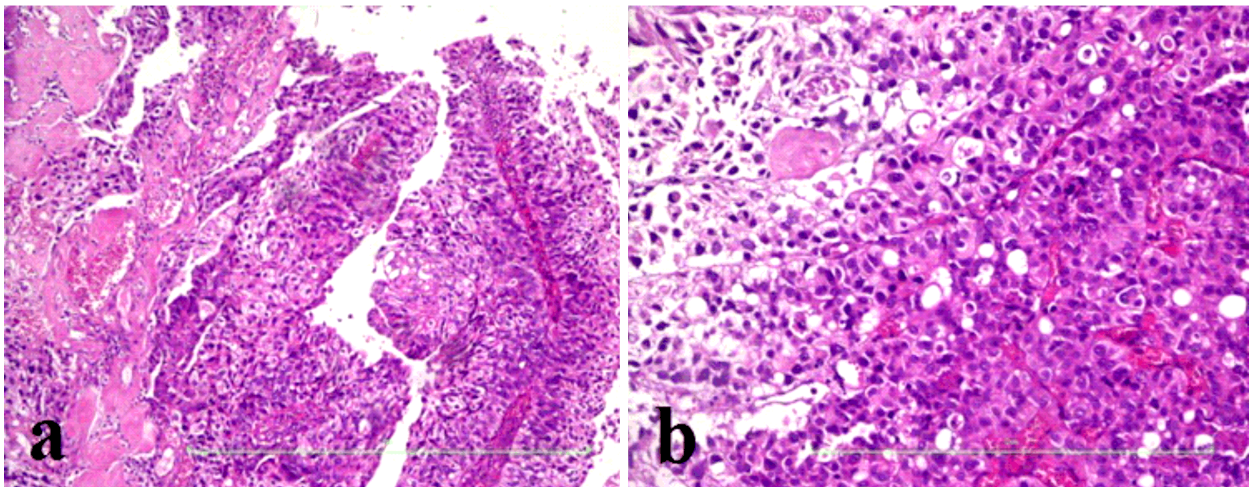

Figure 6 – ***pT1G3 standard monopolar resection: (a and b) High-grade papillary urothelial carcinoma invasive into lamina propria – pT1G3. HE staining: (a) ×100; (b) ×200.***

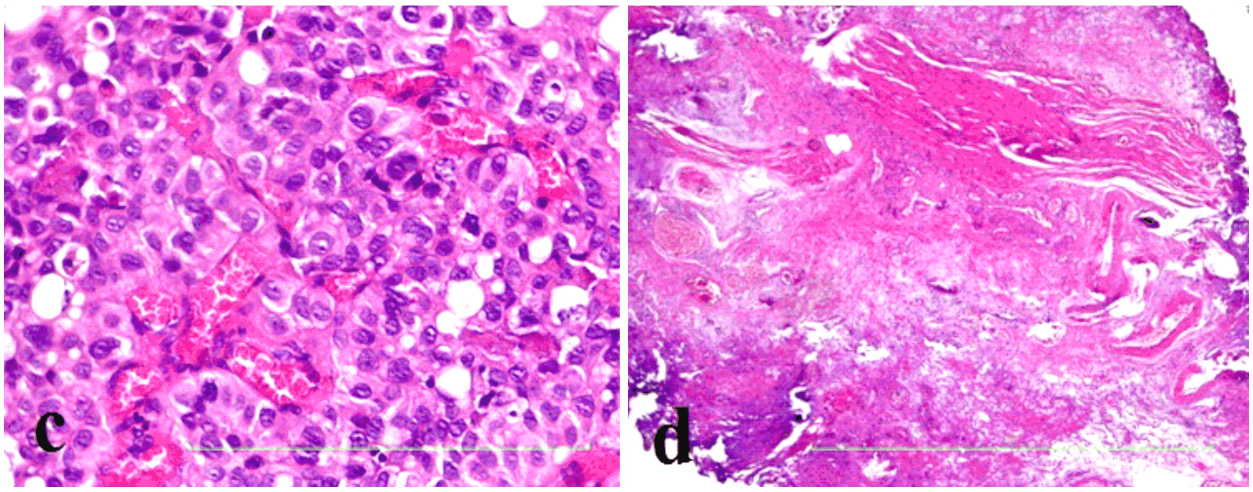

Figure 6 (continued) – ***pT1G3 standard monopolar resection: (c) Marked nuclear pleomorphism and mitotic figures in pT1G3 tumor; (d) Lamina propria and muscularis propria from the tumor bed without invasion. HE staining: (c) ×400; (d) ×40.***

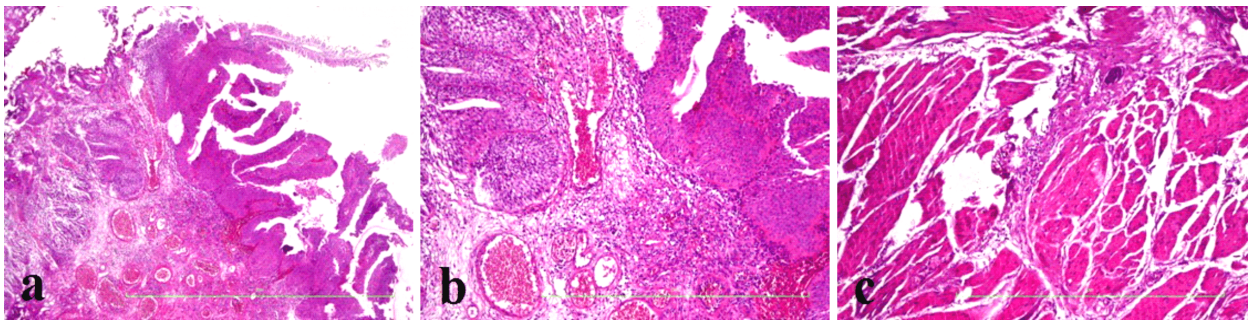

Figure 7 – ***pTaG2 en bloc bipolar resection: (a and b) Low-grade papillary urothelial carcinoma – pTaG2; (c) Muscular layer from the tumor bed without invasion. HE staining: (a) ×40; (b) ×100; (c) ×400.***

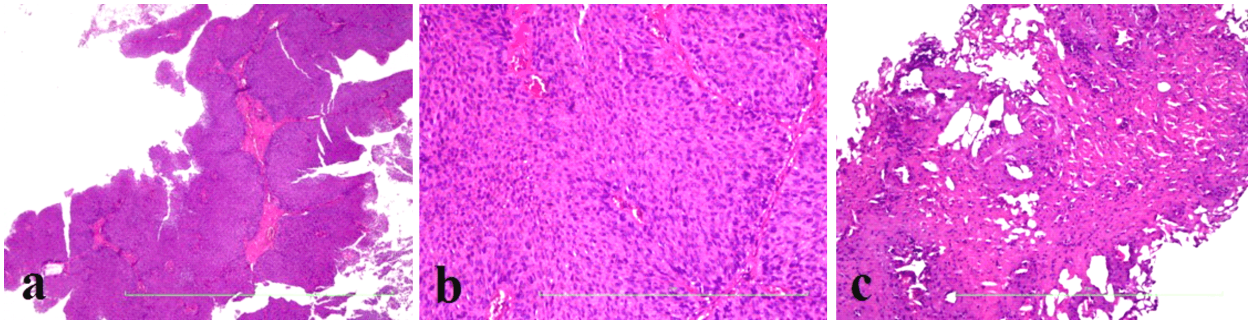

Figure 8 – ***pTaG2 classical monopolar TURBT: (a) Low-grade papillary urothelial carcinoma – pTaG2; (b) pTaG2 – moderate nuclear pleomorphism in non-muscle invasive urothelial carcinoma; (c) Lamina propria and muscularis from the tumor bed without invasion. HE staining: (a) ×40; (b and c) ×200. TURBT: Transurethral resection of bladder tumor.***

Discussions

An important aspect to take into account is the fact that there are some rare types of bladder cancer derived from neuroendocrine tumors like small-cell and large-cell carcinoma of the bladder and the carcinoid tumors with few data reported about the most efficient methods of treatment [27]. Like others neuroendocrine tumors, it has a very aggressive behavior and a poor prognostic, with a rate of survival less than one year [28, 29]. The concept of en bloc bladder tumors' ablation appeared to be increasingly appealing to urologists during the past few years, depending of course on the clinical validation "through the looking glass" of standard TURBT extensively consecrated therapeutic efficiency. Based on these premises, en bloc resection began to be applied as an alternative technique for the removal of NMIBT formations larger than 1 cm in diameter [25]. It was described for the first time as such by Ukai *et al.* in 2000 [21] and further developed into using both laser energy and electrical current as tumor bulk detachment tools, relying on multi-center studies that confirmed the absence of relevant differences concerning the quality of obtained specimens [30].

As far as the surgical safety profile was concerned, the present trial emphasized a significantly reduced rate of obturator nerve reflex adverse events for en bloc resection, when compared to monopolar TURBT (4.4%

versus 11.1%). A possible explanation may be offered by the shorter contact time between the active electrode and the tumor tissue observed during the en bloc approach by comparison to the single-wire loop staged resection. This point of view was shared by most of the available literature in this field of interest, which also underlined the ability of en bloc bladder cancer removal to substantially decrease the frequency of obturator reflexes (0–9% [31–34]), while drawing a parallel to the classical resection (6–25% [31–34]). Following this line, laser based en bloc ablation seems to further ameliorate this surgical parameter [30].

Intuitively speaking, the capacity to primarily resect the tumor base and subsequently detach the lesion in one piece creates the advantage of shorter intervention time, as it avoids the gradual, layer by layer removal by conventional TURBT, additionally prolonged by the necessity to perform repeated hemostasis in order to improve visibility. This technical advantage was found among the results of the present study and previously confirmed by the previously available literature data (22 minutes [35] *versus* 46 minutes [32]).

The reduced intraoperative bleeding and consequently lower mean hemoglobin level drop generally characterize bipolar electrosurgery, when considering a comparison to the conventional monopolar TURBT. In the particular technological setting of en bloc transurethral tumor ablation, the possibility to approach the tumor base directly and not to repeatedly open blood vessels during the staged layer-by-layer removal by classical resection can only add as to the chance of achieving a diminished blood loss. Consequently, both in this clinical analysis (0.28 *versus* 0.76 g/dL), as well as in the already published studies (0.55 *versus* 1.24 g/dL [19]), the mean hemoglobin level drop was shown as significantly ameliorated when applying the en bloc alternative procedure.

The so far outlined superior operative safety profile can be expected to result in a faster postoperative recovery due to the less traumatic en bloc tumor bulk detachment method by bipolar current. As of such, both in the current trial as well as in the previous researches, when compared to the classical TURBT, the bipolar en bloc resection patients benefited from significantly reduced catheterization period (1.9 *versus* 2.8 days and 1.4 days [34] *versus* 4.2 days [32], respectively) and hospital stay (2.3 *versus* 3.1 days and 1.5 days [36] *versus* 4.27 days [33]).

From the point of view of the pathologically confirmed tumor stage, the present findings enlist themselves within the range of literature data despite the rather wide variations (related to the quite heterogeneous patients' category presenting medium size tumors) concerning both pTa (51.1–53.3% and 37.5–54% [37], respectively), as well as pT1 (46.7–48.9% and 46–62.5% [38]) NMIBT stage.

In terms of the quality of the obtained specimens by the two therapeutic approaches, the depth of malignant invasion and complete tumor removal confirmation appear to be reliably supported by both types of transurethral ablation. More precisely, in accordance with the above-mentioned outcomes as well as with the literature reports [24], both en bloc detached tumor bulks and TURBT obtained chips contained part of the detrusor muscle layer, a feature otherwise also preserved by tumor bed biopsies taken at the end of each type of technique. Consequently, it can be underlined that the quality of the histopathological specimens obtained by the deep biopsies of the tumor bed area allowed for an accurate tumor stage to be defined regardless of the applied procedure. Further, along this line, cauterization artifacts were present on specimens obtained by both types of ablation technique in various degrees, without any significant differences. Ultimately, the pathological equivalence of the methods may be concluded based on the similar proportions of pTa and pT1 tumors, resembling capacity of providing a reliable tumor stage and similar cauterization artifacts. Still, the published data regarding this feature remain rather variable, with reported 78–100% presence of muscular fibers in the removed specimens [38, 39] and even occasionally superior en bloc tumor bulks/bases, when compared to monopolar TURBT obtained pieces concerning the inclusion of muscularis propria tissue (100% *versus* 54/70% [37], respectively).

As far as the eventual impact of the en bloc ablation approach is concerned, it may definitely be too early to draw a definite conclusion with regard to eventual advantages from the perspective of recurrent malignancies. Recent studies have shown a relationship between chronic urinary tract infections and the risk of developing bladder cancer [40, 41]. Another important aspect researched lately is the effect of nerve block in reducing postoperative pain [42] and the use of new agents (like botulinum neurotoxins) in manage the chronic pain [43].

While taking into account the presently emphasized analysis, it can be considered as a notable progress the fact that fewer medium term recurrences were described secondary to en bloc resection (17.1% *versus* 27.5%), mostly based on the substantially decreased rate of heterotopic lesions (12.2% *versus* 20%). Other previous reports underlined a satisfactory outcome from the point of view of the oncological findings, with a 20.6% recurrence rate at 20 months for the Thulium laser en bloc resection [44]. More so, during the long-term follow-up (30–40 months), en bloc resection was shown to provide a reduced recurrence rate by comparison to the standard procedure (28.6% *versus* 62.5%) [45]. Our results are in accordance with other studies [18, 19], but evidence-based opinions in this endourological field remain quite contradictory, as other trials did not determine significant differences between the 2 μm continuous-wave laser en bloc resection and monopolar TURBT from the perspective of the overall three year' recurrence rate [32].

Conclusions

Based on the above-acquired clinical data, it can be summarized that that the en bloc plasma-button tumor resection provided the advantages of superior surgical safety, decreased perioperative morbidity and faster postoperative recovery, when compared to the standard monopolar TURBT.

From the point of view of the pathological analysis, the en bloc bipolar electrosurgical detachment preserved the ability of achieving an accurate non-muscle invasive tumor staging, while also proving a match for the conventional resection with regard to the oncological accuracy of the transurethral approach.

From the perspective of the oncological medium-term outcomes, the en bloc resection technique was characterized by significant progresses over the standard TURBT due to the significantly reduced rate of NMIBT recurrences relying of the substantially fewer other site one year' recurrent lesions. A conclusion cannot yet be reached for this presumable oncological advantage, since there is not a uniform point of view in the literature regarding this topic and further clinical research is obviously required.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author
Andrei Niculae, Associate Professor, MD, PhD, Department of Nephrology and Dialysis, "St. John" Emergency Clinical Hospital, Clinical Department No. 3, "Carol Davila" University of Medicine and Pharmacy, 37 Dionisie Lupu Street, Sector 2, 020022 Bucharest, Romania; Phone/Fax +4021–318 07 19, e-mail: niculaeandrei@yahoo.com

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