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Positive surgical margins in nephron-sparing surgery; the great unknown

Dan Spinu
Carol Davila University of Medicine and Farmacy, Central Military Emergency University Hospital, Department of Urology, dan.spinu@yahoo.co.uk

Oana M. Bodean
Emergency University Hospital Bucharest, Department of Obstetrics and Gynecology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, oanamb8@gmail.com

Bogdan Socea
Carol Davila University of Medicine and Pharmacy, Department of Surgery, bogdansocea@gmail.com

Dan Mischianu
Carol Davila University of Medicine and Farmacy, Central Military Emergency University Hospital, Department of Urology, danmischianu@yahoo.co.uk

Ioana Oprea
Central Military Emergency University Hospital, Department of Intensive Care Unit, oprea2oana@yahoo.com

See next page for additional authors

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Authors
Dan Spinu, Oana M. Bodean, Bogdan Socea, Dan Mischianu, Ioana Oprea, and Radu D. Marcu

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Review

Positive surgical margins in nephron-sparing surgery; the great unknown

Dan Spinu[1,2], Oana M. Bodean[3], Bogdan Socea[4], Dan Mischianu[1,2], Ioana Oprea[5], Radu D. Marcu[1,2]*

[1]Department of Urology and [5]Department of Intensive Care Unit, Central Military Emergency University Hospital, Bucharest, Romania
[2]Carol Davila University of Medicine and Farmacy, Department no. III, Bucharest, Romania
[3]Emergency University Hospital, Department of Obstetrics and Gynecology, Bucharest, Romania
[4]Carol Davila University of Medicine and Farmacy, Department of Surgery, Bucharest, Romania

Abstract

There is a currently a general trend towards organ-preserving surgery, and urology is no exception. Specifically, nephron-sparing surgery (NSS) has gained general acceptance for T1a renal cell carcinoma (guidelines recommendations). Moreover T1b, T2 and even T3 stage tumors have been included on the nephron sparing list at some centers. An unresolved issue is that of positive surgical margins (PSM), not only their detection but also the implications for follow up and treatment. This paper highlights data available on risk factors for PSM, their clinical relevance, and possible therapeutic consequences.

From the surgeon's viewpoint, NSS is a daring and risky surgical procedure. Urological guidelines stress the importance of NSS, and thus the trend is moving in that direction. Unresolved, however, is the problem of PSM. Trifecta, MIC, and pentafecta are applicable concepts which attempt to define the optimal endpoint of NSS, but further elaboration is necessary. Specifically, research needs to focus less on the concept of definitive margins and more on their identification and avoidance. Although some studies suggest that PSMs do not influence overall survival rate, the basic idea of preserving tissue that is not cancerous leads to further medical, social, and psychological considerations.

Keywords : renal carcinoma, positive margins, nephron sparing surgery

Highlights

- ✓ Nephron-sparing surgery is considered today by several studies a daring and a risky surgical procedure, with important (medical, psychological and social) implications
- ✓ Positive surgical margin needs to be investigated more not as a definition, but for means of identification/ avoidance that is important for an adequate therapeutic approach.

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✉ *Corresponding author: Marcu Dragos, Central Military Emergency University Hospital, Department of Urology, Bucharest, Romania; email: marcuradudragos@yahoo.com

Introduction

Over the past 20 years, nephron-sparing surgery (NSS) has evolved rapidly and is now considered the standard of care for the treatment of most small renal masses. In accordance with international guidelines, NSS is being widely used to treat tumours less than 4 cm. EAU guidelines recommend partial nephrectomy as the standard procedure for T1a and T1b renal masses in technically feasible cases (1).

NSS seems to have similar oncological outcomes as radical nephrectomy. It is also well suited for minimally invasive surgery either in laparoscopy or using a robotical approach. Initial indications for NSS relied on highly selective cases with single surgical kidney or some tumors with feasible layout for surgery. Due to the technical evolution and the experience of medical staff now available in most centers, NSS is indicated for the T1a stage and may be used within certain limits for other stages of the disease.

This change in therapeutic approach is based primarily on findings indicating that organ-sparing surgery offers the potential for better preservation of renal function and a lower risk of cardiovascular sequelae. Oncological outcomes appear to be equivalent and perioperative morbidity seems to be only minimally higher for nephron-sparing interventions. Unfortunately, there are few studies to assess the significance and impact of the positive surgical margin (PSM) on the patient's prognosis and what therapeutic possibilities exist.

Discussion

Research findings related to nephron-sparing surgery are variable, beginning with case presentations to studies using small series of patients. For instance, Lopez-Costea et al. present a group of 137 patients with NSS, of which 11 had positive surgical margins (2). Along the same line, Kwon et al., in a study of 770 patients who had open partial nephrectomy, reported a total of 57 (7%) with PSMs; two of these had a local recurrence compared with four of 713 who had a negative margin (0.5%). Patients with a low potential for malignancy and PSM did not have a local recurrence (3).

Of the factors that might explain cases of local recurrence having no association with PSMs, the presence of tumour multifocality is relevant. Although more frequent for other tumour types, it is associated with renal cell carcinoma (RCC) and would therefore be considered as an independent variable related to tumour recurrence.

Various procedures that could lessen the risk of a PSM in the final specimen need to be promoted. These include the use of intraoperative ultrasound (US), thereby allowing an adequate safety margin, and hilar clamping that could provide better distinction between healthy and tumorous tissue as well as aid in the correct identification of the calyceal system, with the downside of longer ischaemia time. Regarding this latter point, Yossepowitch et al. noted that, in their series of NSS, more PSMs were found in smaller renal masses (4). This result was probably due to a poor delimitation of healthy and tumourous tissue, the tendency not to use hilar clamping, and limiting surgery solely to the tumour. Concerning renal ischaemia, Yossepovitch et al. suggested that it might cause involution of cells with high metabolic activity. Furthermore, others such as Gallucci et al. proposed selective embolization of large or hilar tumours (5).

The use of powerful haemostatic systems such as an argon-beam or ultrasound scalpel, destroying potential tumour cells in the surgical bed, and the application of haemostatic materials which could induce direct ablation of cells through an inflammatory and/or immunological reaction with cytotoxic capacity all represent strategies that are available for surgical tumour extraction.

Alharbi et al. studied the use of intraoperative ultrasound control of surgical margins during partial nephrectomy (PN). Their study was conducted from January, 2010 to December, 2015 on patients with T1-T2 renal tumors that had undergone PN performed through open, laparoscopic or robot-assisted laparoscopic approaches. Before tumor removal, ultrasound was performed intraoperatively. The tumor was removed with the standardized minimal healthy tissue margin technique. After resection, ultrasound control of the margins was performed. The removed tumor was immersed in a saline solution and US was performed to evaluate in three dimensions whether the tumor capsule was intact. If the margins were negative, hemostasis was performed. If not, an extra rim of renal parenchyma was removed circumferentially to include the entire remaining margin. In their study, 177 PN were included, and the results were compared with the pathology exam. All except one negative US surgical margins were confirmed. In cases where US determination was not feasible, the surgical margins were negative. Overall, all final surgical margins were negative in the pathology exam even when extra rim resection of renal parenchyma was required. In conclusion, intraoperative US had determined the

margin status with 99% sensitivity and 75% specificity. Positive and negative predictive values were also 99% and 75% (6).

A study by Nguyen et al. demonstrated a technique in which the deep tumor margins were marked by a needle implanted in situ under US guidance.

Costabel et al. recently reported their 10-year experience with single kidney patients who had undergone nephron sparing surgery. Of the 45 patients, 4 were found with positive resection margins, and 4 with local recurrence (2 of those with positive margins). Of those 3, they were in T1a and one in T1b. Most important was that the extemporaneous exam was negative in all four cases, a thing that does not only appear in their work (7).

One of the most valuable materials and one of the few papers dealing with this theme is written by Steinestel et al. Their review covers a period of 15 years. The authors identified one of the risk factors for PSM as the unique kidney condition (either functional or anatomical). PSM rates of 9 to 28% are described here (8).

Tumor size is a risk factor about which there is no definitive agreement yet. Some authors claim that small tumor masses present higher risk, whereas others state larger ones present higher risk. Some authors contend that size is not a risk factor in itself. A second factor considered by the authors is the tumor topography. Although no consensus exists, it is generally accepted that medioreal tumor formations present a higher risk of PSM.

Reliance on frozen sections, which theoretically should be useful to the urologist, unfortunately presents marginal results and generally does not influence the prognosis of the disease and the rate of detection of the positive margins (9). Microscopic examination performed by an intraoperative surgeon appears to have better results. More recently, there is a cytology proposition that delivers results consistent with the final histopathological exam.

The impact of PSM on local relapse and patient survival is controversial. Studies claim that PSM is a predictor of relapse and poor prognosis for the disease. On the other hand, some authors claim that PSM has no value in tracking the patient. The general assumption is that microscopic PSMs do not present a risk factor for patient survival but that, nevertheless, such situations should be avoided. Most positions recommend a conservative rather than aggressive approach toward surgery.

Wang et al. evaluated the laparoscopic retroperitoneal approach on 53 patients. The resection limit was 5 mm and one patient presented PSM but no relapse at 56 months. Their PSM recommendation includes surveillance and imaging surveillance (10).

On 63 patients who underwent laparoscopic partial nephrectomy Osaka et al. found 4 patients (6,3%) with positive surgical margins. The aim of their study was to evaluate the predictors of trifecta outcomes for laparoscopic partial nephrectomy for T1a renal masses (11).

Joniau et al. studied the outcome of nephron-sparing surgery for T1b renal cell carcinoma on a group of 67 patients (average age – 62) with T1b carcinoma tumors 4-7 cm. They monitored tumor characteristics, surgical indication, complications of recurrence, and time-to-death. Positive margins were diagnosed in 4 patients (6%). None of these patients developed distant or local metastases within 3 years. Of these patients, 2 ranked Fuhrman III and the other 2 Fuhrman II grades. None had any surgical indication for reintervention. The renal ischemia time was 14 minutes on average, using both the renal pedicle clamping method and hypothermia (12).

Smith et al. developed a technique for tumor enucleation for renal cell carcinoma involving the use of tumor pseudocapsules to remove as little healthy kidney tissue as possible. Traditionally, the 1 cm margin of the enucleated tumor was considered optimal, but new studies have since contradicted this assumption, with edges under 1 cm being equally safe. Positive margins were found in about 7% of cases according to other studies. Analysis of these patients has shown little influence on the survival rate (13).

The British Association of Urological Surgeons performed their own set of analyses: their study included 86 UK centers where 1044 partial nephrectomies were practiced within one year. Testing of the resection margins was done in 68% of cases, of which only 7% were positive, and most positive margins were found in stages T3 - 48%, compared to 6% in T1a. According to international guidelines for tumor formations below 4 cm, the primary indication is partial nephrectomy with results as good as radical nephrectomy even with the presence of positive margin in 6% of the cases (14). Positive margins were mainly based on tumor size; the surgical technique chosen did not affect their appearance. In conclusion, these procedures involved higher costs (more frequent imaging invasions), as the oncologists worried about long-term relapse or metastasis.

Another studied attempted to follow the evolution of a larger tumor T3 stage. This study followed the partial nephrectomy characteristics in renal tumors in the T3bNxMx stage with limited tumor renal vein thrombosis. Specifically, 305 patients were studied between 2004 and 2009, and of these, 2-7% had tumoral thrombus in the renal vein and became the subject of their study. All patients had one morpho-functional kidney, the main reason for partial nephrectomy. On none of the 7 patients were positive resection margins found. Only one patient required surgical reintervention with radical nephrectomy, and he was forced to remain on dialysis for the remainder of his life. No local metastasis or local recurrence was detected in any patient within 30 months after surgery. The approach used was mainly pararectal. Studies have showed a 5-year survival rate of between 47% and 69% (15).

Trifecta is defined as negative surgical margins, zero perioperative complications, and warm ischaemia time < 25 minutes. Zargar et al. enhanced this criterion, adding 90% glomerular rate preservation and no chronic disease stage upgrading. Other authors coined the term MIC (negative Margin, Ischaemia no<20 minutes and no major complications) (16, 17).

Kim et al. found a rate of positive surgical margins in T1a of 5% versus 6,6% in T1b. The rate of achievement of Trifecta for T1a and T1b renal mass was 65.3% and 43.3%, respectively (P = 0.017), and the rate of achievement of Pentafecta was 38.3% and 26.7%, respectively (P = 0.172). There is large variation in terms of the rate of achievement for Trifecta, ranging from 32% to 81%. The overall PSM was 5,8 %, which is comparable to other studies (18).

Logically the use of partial nephrectomy for higher risk patients shows superior rates of positive surgical margins. Maurice et al., in a large retrospective study, reviewed the outcomes of partial nephrectomy in patients with more than one adverse pathological feature, defined as follows: advanced disease pT3, unfavorable histology (sarcomatoid, collecting duct, or medullary subtype), high nuclear grade, or any of the above three criteria. These researchers found a 8,4% positive surgical margins rate, which increased over time (19).

However only surgical volume and the robotic approach seem to be independent predictors for positive surgical margins after partial nephrectomy (20). Positive surgical margin is an independent factor of local recurrence but does not impact survival (21).

Simon et al. performed laparoscopic partial nephrectomy with selective control of the renal parenchyma by using a special clamp. Their study tracked patients who had undergone nephrectomy using a new type of vascular clamping that allows selective control of renal parenchyma. The study included patients with kidney tumors under 4 cm in the T1a and T1b stages, and Furhman grade 2 or 3. A Nussbaum special clamp was used, which allowed better control of renal parenchyma. Three patients aged 60, 64, and 77 years were considered: none had positive margins. In these, the tumor formation was located peripherally, which allowed the use of such a clamp. The major advantage of using this clamp is that ischemia occurs only at the level of the tumor (22).

Some authors report no or very few PSMs. In a retrospective comparison study on 102 patients with open and robotic partial nephrectomy, Omer et al. found only one case of positive surgical margin (23). This finding is consistent with the report of Tufek et al. who on 50 patients with robotic assisted partial nephrectomy found no positive surgical margins. They used in every case an intraoperatory ultrasonography with excellent results. Novel techniques with promising results are also emerging, such as near-infrared fluorescence after intravenous injection of indocyanine green (24, 25). Ricciardulli et al., on 316 patients with laparoscopic and robotic partial nephrectomy, found positive surgical margins in 5% and 0% respectively (26).

Volpe et al. studied perioperative and renal functional outcomes of elective robot-assisted partial nephrectomy (RAPN) for renal tumors with high surgical complexity. The purpose of their study was preoperative and postoperative follow-up on 44 patients who underwent robotic assisted partial laparoscopic nephrectomy. Twenty-three patients were in the T1b stage, the rest in T1a stage. Of these, only 2 were diagnosed with positive resection margins (4%), below the median described in the literature. Patients were followed radiologically for 23 months without local recurrence or remote metastases. Prior to surgery, all patients benefited from CT, X-ray, and ultrasonography, which placed the diagnosis of renal tumor to less than 4 cm, partial laparoscopic nephrectomy being currently the gold standard for the treatment of this type of tumor. Uric acid and hemoleucogram levels were monitored both before and after surgery. The histopathological examination set the diagnosis of benign tumors in 10 cases. The effectiveness of this type of surgery compared to classical partial nephrectomy has been demonstrated, with simple laparoscopic, shortened operation time, lower blood loss, and faster recovery of the patient (27).

Jong et al. compared the surgical margin in open vs robotic partial nephrectomy. The results were interesting, given that positive surgical margins were found in 1,8% of open partial nephrectomies versus 1,3% in robotic partial nephrectomies, that is, surgical margins were significantly narrower for the robotic surgery. Of the 2 patients who presented local recurrence, both had negative surgical margins (28).

For years, a 1cm margin was considered oncologically safe. But recent studies have demonstrated that 5 mm margin may also be safe (29). The authors proposed a 3 mm margin but sufficient data are not available to support this conclusion (30). On the other hand, Liu et al., in a study on 118 T1 patients in three groups—open radical nephrectomy, open partial nephrectomy and laparoscopic partial nephrectomy (31)—found that positive surgical margins were significantly lower in the open partial nephrectomy than in laparoscopic partial nephrectomy.

Conclusions

Generally, the positive surgical margin may lead to local recurrence of neoplasia. Although the recurrence is rare (2,2%), nephron-sparing surgery is nevertheless quite difficult (32), and is complicated by the fact that it involves a reintervention. Even more puzzling is the variate time of appearance of the neoplasia, ranging from 3 months to 45 years (33, 34). There is currently no standard strategy or guideline for this type of disease.

Few studies have investigated the treatment strategy for this neoplasic pathology. Based on 47 patients, Johnson et al. reported an overall major perioperative complication rate of 19.6%, higher than the rates reported in PN series of surgically naive patients. However, this rate is understandable, given that each anatomical plane is changed and substantial tissue scarring occurs (35). Renal clear cell carcinoma is radio resistant and thus the use of radiotherapy is of little or no use.

Although surgery remains the gold standard, data suggest that (neo)adjuvant chemotherapy can be beneficial. Unfortunately, even with this combination, the rate of progression is catastrophic as highlighted by Margulis et al. (36, 37). The goal of this paper in describing several treatment options was to underline the importance of identification of PSM, despite the lack of a specific correlation between PSM and local relapse. Moreover later complications which involve solitary kidney pathology and even dyalisis can be avoided (38-43).

Intraoperatory ultrasound is the only method which is used sufficiently to ascertain an impact on outcomes. Although cytology shows promising results, it is typically limited by staff experience. The use of indocyanine green is promising though still not widespred.

Even more intriguing is the differential diagnosis of this pathology with retroperitoneal space pathology (44, 45). Positive surgical margin needs to be investigated more not as a definition, but for means of identification/ avoidance that is important for an adequate therapeutic approach.

References

1. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Mulders P, Powles T, Staehler M, Volpe A, Bex A. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol*. 2015; 67(5): 913–24. PMID: 25616710, DOI: 10.1016/j.eururo.2015.01.005
2. Lopez-Costea MA, Fumadó L, Lorente D, Riera L, Miranda EF. Positive margins after nephron-sparing surgery for renal cell carcinoma: long-term follow-up of patients on active surveillance. *BJU Int*. 2010; 106(5): 645-8. PMID: 20067450, DOI: 10.1111/j.1464-410X.2009.09174.x
3. Kwon EO, Carver BS, Snyder ME, Russo P. Impact of positive surgical margins in patients undergoing partial nephrectomy for renal cortical tumours. *BJU Int*. 2007; 99(2): 286-9. PMID: 17155985, DOI: 10.1111/j.1464-410X.2006.06623.x
4. Yossepowitch O, Thompson RH, Leibovitch BC, Eggener SE, Pettus JA, Kwon ED, Herr HW, Blute ML, Russo P. Predictors and oncological outcomes following positive surgical margins at partial nephrectomy. *J Urol.* 2008; 179(6): 2158–63. PMID: 18423758, DOI: 10.1016/j.juro.2008.01.100
5. Gallucci M, Guaglianone S, Carpanese L, Papalia R, Simone G, Forestiere E, Leonardo C. Superselective embolization as first step of laparoscopic partial nephrectomy. *Urology*. 2007; 69(4): 642-5; discussion 645-6. PMID: 17445641, DOI: 10.1016/j.urology.2006.10.048
6. Alharbi FM, Chahwan CK, Le Gal SG, Guleryuz KM, Tillou XP, Doerfler AP. Intraoperative ultrasound control of surgical margins during PN. *Urol Ann*. 2016; 8(4): 430–3. PMID: 28057986, DOI: 10.4103/0974-7796.192107

7. Costabel JI, Marchinena PG, Tirapegui F, Dantur A, Jurado A, Gueglio G. Functional and oncologic outcomes after nephron-sparing surgery in a solitary kidney: 10 years of experience. *Int Braz J Urol*. 2016; 42(2): 253-61. PMID: 27256179
8. Steinestel J, Steffens S, Steinestel K, Schrader AJ. Positive surgical margins in nephron-sparing surgery: risk factors and therapeutic consequences. *World J Surg Oncol*. 2014; 12: 252. PMID: 25103683, DOI: 10.1186/1477-7819-12-252
9. Marszalek M, Carini M, Chlosta P, Jeschke K, Kirkali Z, Knüchel R, Madersbacher S, Patard JJ, Van Poppel H. Positive surgical margins after nephron-sparing surgery. *Eur Urol*. 2012; 61(4): 757–63. PMID: 22136987, DOI: 10.1016/j.eururo.2011.11.028
10. Wang J, Qi L, Zu X, Chen M. Application of retroperitoneal laparoscopic partial nephrectomy for renal cell carcinoma of the early stage. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2012; 37(5): 485-90. PMID: 22659661, DOI: 10.3969/j.issn.1672-7347.2012.05.010
11. Osaka K, Makiyama K, Nakaigawa N, Yao M. Predictors of trifecta outcomes in laparoscopic partial nephrectomy for clinical T1a renal masses. *Int J Urol*. 2015; 22(11): 1000-5. PMID: 26251228, DOI: 10.1111/iju.12893
12. Joniau S, Vander Eeckt K, Srirangam SJ, Van Poppel H. Outcome of nephron-sparing surgery for T1b renal cell carcinoma. *BJU Int*. 2009; 103(10): 1344-8. PMID: 19040528, DOI: 10.1111/j.1464-410X.2008.08230.x
13. Smith ZL, Malkowicz SB. Tumor Enucleation for Renal Cell Carcinoma. *J Kidney Cancer VHL*. 2015; 2(2): 64–69. PMID: 28326260, DOI: 10.15586/jkcvhl.2015.27
14. Fernando A, Fowler S, O'Brien T; British Association of Urological Surgeons (BAUS). Nephron-sparing surgery across a nation outcomes from the British Association of Urological Surgeons 2012 national partial nephrectomy audit. *BJU Int*. 2016; 117: 874–82. PMID: 26469291, DOI: 10.1111/bju.13353
15. Kolla SB, Ercole C, Spiess PE, Pow-Sang JM, Sexton WJ. Sexton Nephron-sparing surgery for pathological stage T3b renal cell carcinoma confined to the renal vein. *BJU Int*. 2010; 106(10): 1494-8. PMID: 20230378, DOI: 10.1111/j.1464-410X.2010.09293.x
16. Porpiglia F, Bertolo R, Amparore D, Fiori C. Margins, ischaemia and complications rate after laparoscopic partial nephrectomy: impact of learning curve and tumour anatomical characteristics. *BJU Int*. 2013; 112(8): 1125–32. PMID: 23937616, DOI: 10.1111/bju.12317
17. Buffi N, Lista G, Larcher A, Lughezzani G, Ficarra V, Cestari A, Lazzeri M, Guazzoni G. Margin, ischemia, and complications (MIC) score in partial nephrectomy: a new system for evaluating achievement of optimal outcomes in nephron-sparing surgery. *Eur Urol*. 2012; 62(4): 617–8. PMID: 22704367, DOI: 10.1016/j.eururo.2012.06.001
18. Kim LH, Raheem AA, Shin TY, Alabdulaali I, Yoon YE, Han WK, Rha KH. Comparison of Trifecta and Pentafecta Outcomes between T1a and T1b Renal Masses following Robot-Assisted Partial Nephrectomy (RAPN) with Minimum One Year Follow Up: Can RAPN for T1b Renal Masses Be Feasible? *PLoS One*. 2016; 11(3): e0151738. PMID: 26987069, DOI: 10.1371/journal.pone.0151738
19. Maurice MJ, Zhu H, Kim SP, Abouassaly R. Increased use of partial nephrectomy to treat high-risk disease. *BJU Int*. 2016; 117: E75–E86. PMID: 26305770, DOI: 10.1111/bju.13262
20. Bernhard JC, Pantuck AJ, Wallerand H, Crepel M, Ferrière JM, Bellec L, Maurice-Tison S, Robert G, Albouy B, Pasticier G, Soulie M, Lopes D, Lacroix B, Bensalah K, Pfister C, Thuret R, Tostain J, De La Taille A, Salomon L, Abbou C, Colombel M, Belldegrun AS, Patard JJ. Predictive factors for ipsilateral recurrence after nephron-sparing surgery in renal cell carcinoma. *Eur Urol*. 2010; 57(6): 1080–6. PMID: 20188458, DOI: 10.1016/j.eururo.2010.02.019
21. Bensalah K, Pantuck AJ, Rioux-Leclercq N, Thuret R, Montorsi F, Karakiewicz PI, Mottet N, Zini L, Bertini R, Salomon L, et al. Positive surgical margin appears to have negligible impact on survival of renal cell carcinomas treated by nephron-sparing surgery. *Eur Urol*. 2010; 57(3): 466–71. PMID: 19359089, DOI: 10.1016/j.eururo.2009.03.048
22. Simon J, Bartsch G Jr, Finter F, Hautmann R, de Petriconi R. Laparoscopic partial nephrectomy with selective control of the renal parenchyma: initial experience with a novel laparoscopic clamp. *BJU Int*. 2009; 103(6): 805-8. PMID: 19007377, DOI: 10.1111/j.1464-410X.2008.08112.x
23. Acar Ö, Işık EÖ, Mut T, Sağlıcan Y, Onay A, Vural M, Musaoğlu A, Esen T. Comparison of the

trifecta outcomes of robotic and open nephron-sparing surgeries performed in the robotic era of a single institution. *Springerplus*. 2015; 4: 472. PMID: 26361573, DOI: 10.1186/s40064-015-1274-2

24. Mourmouris P, Doganca T, Obek C, Argun OB, Tuna MB, Keskin MS, Kural AR. Robot-Assisted Partial Nephrectomy for T1b Tumors: Strict Trifecta Outcomes. *JSLS*. 2017; 21(1). pii: e2016.00113. PMID: 28352149, DOI: 10.4293/JSLS.2016.00113
25. Knopf JK, Silvers CR, Marshall J, Cardin A, Wood RW, Reeder JE, Erturk E, Madeb R, Yao J, Singer EA, Rashid H, Wu G, Messing E, Golijanin D. Near infrared fluorescence imaging after intravenous indocyanine green: initial clinical experience with open partial nephrectomy for renal cortical tumors. *Urology*. 2012; 79(4): 958 –64. PMID: 22336035, DOI: 10.1016/j.urology.2011.10.016
26. Ricciardulli S, Ding Q, Zhang X, Li H, Tang Y, Yang G, Wang X, Ma X, Breda A, Celia A. Evaluation of laparoscopic vs robotic partial nephrectomy using the margin, ischemia and complications score system: A retrospective single center analysis. *Arch Ital Urol Androl*. 2015; 87(1): 49-55. PMID: 25847897, DOI: 10.4081/aiua.2015.1.49
27. Volpe A, Garrou D, Amparore D, De Naeyer G, Porpiglia F, Ficarra V, Mottrie A. Perioperative and renal functional outcomes of elective robot-assisted partial nephrectomy (RAPN) for renal tumours with high surgical complexity. *BJU Int*. 2014; 114(6): 903–9. PMID: 24673750, DOI: 10.1111/bju.12751
28. Oh JJ, Lee JK, Kim K, Byun SS, Lee SE, Hong SK. Comparison of the Width of Peritumoral Surgical Margin in Open and Robotic Partial Nephrectomy: A Propensity Score Matched Analysis. *PLoS One*. 2016; 11(6): e0158027. PMID: 27336438, DOI: 10.1371/journal.pone.0158027
29. Zucchi A, Mearini L, Mearini E, Costantini E, Vivacqua C, Porena M. Renal cell carcinoma: histological findings on surgical margins after nephron sparing surgery. *J Urol*. 2003; 169(3): 905–8. PMID: 12576810, DOI: 10.1097/01.ju.0000046779.58281.c4
30. Li QL, Guan HW, Zhang QP, Zhang LZ, Wang FP, Liu YJ. Optimal margin in nephron-sparing surgery for renal cell carcinoma 4 cm or less. *Eur Urol*. 2003; 44(4): 448–51. PMID: 14499679
31. Liu TY, Li J, Wen XH, Zhang H, Gui Q. The efficacy of open nephron-sparing surgery in the treatment of complex renal cell carcinoma. *Eur Rev Med Pharmacol Sci*. 2016; 20(19): 3959-64. PMID: 27775806
32. Constantin VD, Socea B, Popa F, Carâp AC, Popescu G, Vlădescu T, Ceauşu Z, Berteşteanu ŞV, Ceauşu MC. A histopathological and immunohistochemical approach of surgical emergencies of GIST. An interdisciplinary study. *Rom J Morphol Embryol*. 2014; 55(2 Suppl): 619-27. PMID: 25178335
33. Featherstone JM1, Bass P, Cumming J, Smart CJ. Solitary, late metastatic recurrence of renal cell carcinoma: two extraordinary cases. *Int J Urol*. 2006; 13(12): 1525-7. PMID: 17118029, DOI: 10.1111/j.1442-2042.2006.01577.x
34. Tapper H, Klein H, Rubenstein W, Intriere L, Choi Y, Kazam E. Recurrent renal cell carcinoma after 45 years. *Clin Imaging*. 1997; 21(4): 273-5. PMID: 9215475
35. Johnson A, Sudarshan S, Liu J, Linehan WM, Pinto PA, Bratslavsky G. Feasibility and outcomes of repeat partial nephrectomy. *J Urol*. 2008; 180(1): 89-93; discussion 93. PMID: 18485404, DOI: 10.1016/j.juro.2008.03.030
36. Margulis V, McDonald M, Tamboli P, Swanson DA, Wood CG. Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. *J Urol*. 2009; 181(5): 2044-51. PMID: 19286220, DOI: 10.1016/j.juro.2009.01.043
37. Vlăsceanu AM, Petraru C, Baconi D, Ghica M, Arsene A, Popa L, Nicolae A, Drăgoi C, Pavalache G. Quantitative relationships of urinary cotinine levels in smoking diabetic patients. *Farmacia*. 2015; 63(3): 349-56.
38. Peride I, Rădulescu D, Niculae A, Ene V, Bratu OG, Checheriță IA. Value of ultrasound elastography in the diagnosis of native kidney fibrosis. *Med Ultrason*. 2016; 18(3): 362-9. PMID: 27622414
39. Niculae A, Peride I, Marinescu-Paninopol A, Vrabie CD, Ginghină O, Jecan CR, Bratu OG. Renal artery bilateral arteriosclerosis cause of resistant hypertension in hemodialysed patients. *Rom J Morphol Embryol*. 2016; 57(2): 591-4. PMID: 27516040
40. Checheriţă IA, Smarandache D, Rădulescu D, Peride I, Bratu O, Ciocâlteu A, Sebe I, Lascăr I. Calcific uremic arteriolopathy in hemodialyzed

patients. *Chirurgia (Bucur).* 2013; 108(5): 736-40. PMID: 24157123

41. Radulescu D, Balcangiu Stroescu A, Pricop C, Geavlete B, Negrei C, Bratu O, Ginghina O, Vacaroiu I. Vitamin K influence on cardiovascular mortality in chronic hemodialysed patients. *Rev Chim. (Bucharest) 2017;* 68(1): 52-54.
42. Niculae A, Peride I, Vinereanu V, Rădulescu D, Bratu OG, Geavlete BF, Checheriță IA. Nephrotic syndrome secondary to amyloidosis in a patient with monoclonal gammopathy with renal significance (MGRS). *Rom J Morphol Embryol*. 2017; 58(3): 1065-8. PMID: 29250691
43. Sinescu RD, Niculae A, Peride I, Vasilescu F, Bratu OG, Mischianu DL, Jinga M, Checheriţă IA. Uterus neuroendocrine tumor - a severe prognostic factor in a female patient with alcoholic cirrhosis undergoing chronic hemodialysis. *Rom J Morphol Embryol*. 2015; 56(2): 601-5. PMID: 26193237
44. Bratu O, Mischianu D, Spanu D, Barla R, Hoara P, Constantinoiu S. Paraneoplastic syndrome in primitive retroperitoneal tumours. *Chirurgia (Bucur).* 2013; 108(1): 26-31. PMID: 23464765
45. Constantinoiu S, Bîrlă R, Iosif C, Cociu L, Gîndea C, Hoară P, Bratu O, Ruşitoru L. Difficulties in diagnosis and surgical treatment of a giant retroperitoneal lipoma. *Chirurgia (Bucur).* 2009; 104(3): 363-7. PMID: 19601474