



Platinum Priority – Kidney Cancer

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Radical Nephrectomy with and without Lymph-Node Dissection: Final Results of European Organization for Research and Treatment of Cancer (EORTC) Randomized Phase 3 Trial 30881

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Abstract

Background: Until now the therapeutic value of lymphadenectomy for renal-cell carcinoma has remained controversial. Several studies attempting to solve this controversy have been published, but none of them were set up as prospective randomized trials.

Objective: To assess whether a complete lymph-node dissection in conjunction with a radical nephrectomy for renal-cell cancer is more effective than a radical nephrectomy alone.

Design, setting, and participants: In 1988, the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group started a randomized phase 3 trial comparing radical nephrectomy with a complete lymphadenectomy to radical nephrectomy alone. After the renal-cell carcinoma was judged to be NOMO and resectable, patients were randomly selected prior to surgery to undergo either a radical nephrectomy with a complete lymph-node dissection or to undergo a radical nephrectomy alone. Postoperatively all patients were followed for progression of disease and mortality.

Intervention: All patients underwent a radical nephrectomy with or without a complete lymph-node dissection.

Measurements: All patients were postoperatively evaluated for time-to-progression, overall survival, and progression-free survival. Time-to-event curves were estimated based on the Kaplan-Meier method and compared using a two-sided log-rank test.

Results and limitations: Of the 772 patients selected for randomization, 40 were not eligible for the study. 383 patients were randomly selected to receive a complete lymph-node dissection together with a radical nephrectomy, and 389 patients were randomly selected to undergo a radical nephrectomy alone. The complication rate did not differ significantly between the two groups. Complete lymph-node dissections in 346 patients revealed an absence of lymph-node metastases in 332 patients. The study revealed no significant differences in overall survival, time to progression of disease, or progression-free survival between the two study groups.

Conclusions: This study shows that, after proper preoperative staging, the incidence of unsuspected lymph-node metastases is low (4.0%) and that, notwithstanding a possible relationship to this low incidence rate, no survival advantage of a complete lymph-node dissection in conjunction with a radical nephrectomy could be demonstrated.

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1. Introduction

Nodal involvement is one of the major factors influencing the prognosis of cancer patients, including carcinoma of the kidney. In the various series reported in the literature, the overall 5-yr survival rates for Robson stage I renal-cell carcinoma (tumor confined to the kidney) ranged between 65% and 93%, and for stage II renal-cell carcinoma (extension to perirenal fat but within Gerota's fascia) survival rates ranged between 44% and 68% [1]. These survival rates decreased considerably when lymph-node metastases were present. In this group of patients, the overall 5-yr survival rates ranged from 0% to 20% [2].

The incidence of lymph-node metastases in renal cancer ranges from 13% to >32% [3–10], and this incidence increases with the stage of the tumor [11].

Lymph-node dissection has resulted in the detection of lymphatic metastases in 7.5–22.5% of patients who have no other evidence of metastatic disease [6,12], and there is little doubt about the value of regional lymph-node dissection as a staging procedure. More recent studies, however, have shown that, with proper staging techniques, the number of unsuspected lymph-node metastases detected at surgery is considerably less [13].

Because renal carcinoma metastasizes by both blood-borne and lymphatic routes, regional lymphadenectomy has been proposed as a method of improving the results of surgical therapy. However, the therapeutic value of lymphadenectomy for renal-cell carcinoma is still controversial. Lymph-node dissection might improve the prognosis of renal-cell carcinoma, but factors such as the extent of the lymph-node dissection, the possible increase in operative morbidity and mortality, and the incidence of nodal metastases should be investigated in a well-planned prospective study. For this reason, the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group initiated a study in 1988 in which all these factors were studied in a randomized, prospective manner. Preliminary results of this study, including morbidity and the incidence of unsuspected lymph-node metastases, have been published previously [13]. The final updated results of this study, including survival data, are presented in this paper.

2. Methods

2.1. Trial design and analysis

The trial was set up as a phase 3 study in which the patients were randomly selected at the EORTC Data Center to undergo

a radical nephrectomy alone or a radical nephrectomy plus a complete lymph-node dissection. The randomization was stratified by center using the minimization technique. The primary end point of this trial was the duration of survival. It was presumed that the group of patients who would undergo a radical nephrectomy without a lymph-node dissection would have a 5-yr survival rate of approximately 70% [14]. Calculations revealed that, in order to detect an increase of 15% in the 5-yr survival rate to 85% in patients having a radical nephrectomy plus a complete lymph-node dissection, a total of 62 deaths were required statistically. Originally this study planned to enroll 276 eligible and evaluable patients (138 in each arm) to be followed for an average of 5 yr ($\alpha = 0.05$; $\beta = 0.10$). However, since the accrual of patients was rapid, an increase in the total number of patients to approximately 700 was made in order to be able to detect a difference of 10% in an intent-to-treat analysis. Time-to-event curves were estimated based on the Kaplan-Meier method and compared using a two-sided log-rank test.

2.2. Patients

Tumor staging was done according to the 1978 TNM system [15]. To be eligible for the study, all patients had to have a resectable, clinically staged N0 M0 adenocarcinoma of the kidney. Tumor categories 1–3 were allowed, provided that a radical nephrectomy with curative intent was feasible. Patients who had clinically detectable lymph-node metastases or distant metastases before surgery were ineligible and were excluded from the study. Preoperatively, all patients had a computed tomography (CT) scan of the abdomen, an intravenous urogram (IVU), and a chest X-ray. Required blood examinations included at least the following: erythrocyte sedimentation rate (ESR), urea, creatinine, and alkaline phosphatase.

2.3. Surgery

In each patient a radical nephrectomy was done via a thoracoabdominal, a lumboabdominal, or a midline incision. In the patients in the treatment group that received only a radical nephrectomy, a simple flank incision was allowed. In the patients who were in the treatment group that received both a complete lymph-node dissection and radical nephrectomy, the dissection extended from the crus of the diaphragm inferiorly to the bifurcation of the aorta or vena cava. For right-sided tumors, dissections of the lateral caval, precaval, postcaval, and interaortocaval nodes were performed. For left-sided tumors dissections of the left para-aortic nodes, the left diaphragmatic nodes, and the preaortic nodes were performed. When previously undetected enlarged lymph nodes were found during operation in a patient in the nephrectomy-only treatment group, lymph-node biopsy, or sampling was done for staging purposes, but a complete lymph-node dissection was not performed.

With the specimen, the pathologist received a scheme of the surgical situation which indicated the site of the tumor, the site of the removed lymphatic tissue, and the site of the clinically suspected lymph nodes removed during operation.

The resected strands of lymphatic tissue were examined in such a way that all lymph nodes were included. The site and size of each lymph-node metastasis was recorded. All material was processed according to the routine of the local pathology laboratory.

Postoperatively, the patients were checked every 3 mo during the first year, every 4 mo during the second and third years, and every 6 mo thereafter. Each visit included a physical examination, laboratory examinations, and a chest X-ray. A CT scan was made yearly, and more frequently when progression was suspected.

3. Results

From May 1988 until September 1991, 772 patients with a clinically locally confined tumors of the kidney were enrolled in the study. 389 patients were randomly selected to have a radical nephrectomy without a lymph-node dissection. 383 patients were randomly selected to undergo a radical nephrectomy with a complete lymph-node dissection. 40 patients were not eligible, mainly due to an incorrect disease stage or histopathology, thus leaving 732 eligible patients, 370 in the radical nephrectomy-only group and 362 in the group undergoing a radical nephrectomy plus lymph-node dissection.

Baseline characteristics of the two treatment groups as well as their tumor characteristics were presented previously [13], as were surgical aspects and complications. Tables 1–3 show updated summaries of the baseline characteristics and the surgical complications. The extension of the operation caused by the lymph-node dissection had no real impact on the complication rate.

Table 1 – Patient characteristics at randomization*

	Without lymph-node dissection		With complete lymph-node dissection	
	n	%	n	%
Total	389		383	
Ineligible	19	5	21	6
Sex				
Male	240	65	208	57
Female	127	35	159	43
Median age	61 yr		61 yr	
WHO performance status				
0	315	86	310	84
1	45	12	46	13
2–4	7	2	11	3

WHO = World Health Organization.
* Data are missing for 22 patients from the treatment group that did not receive lymph-node dissection and for 16 patients from the treatment group that did receive lymph-node dissection.

Table 2 – Clinical tumor characteristics at study enrollment

	Without lymph-node dissection		With complete lymph-node dissection	
	n	%	n	%
Site of the tumor				
Right side	195	53	198	54
Left side	172	47	169	46
Tumor category				
T1	23	6	34	9
T2	242	66	221	60
T3	101	28	112	31
Tumor diameter, cm				
Median	6		5.5	
Maximum	20		19	

Information on the lymph-node status was available in 346 of 383 patients in the group that received a complete lymph-node dissection (Table 4). Fifty-one of these patients had palpably enlarged lymph nodes during surgery. Of these 51 patients, 10 patients (20%) had lymph-node metastases, while only 4 out of 311 patients (1%) without palpable lymph nodes were shown to have metastases in the lymph nodes ($p < 0.001$). Thus 96% of the patients had no lymph-node metastases shown by pathological examination of the resected lymph nodes.

Of the 365 patients who underwent a nephrectomy without lymph-node dissection, 33 patients (9.0%) had palpably enlarged lymph nodes during surgery. These lymph nodes were biopsied or taken out for staging purposes, but no formal lymph-node dissection was done. At biopsy, lymph-node metastases were found in tissue from only 4 of these 33 patients (12.1%).

Survival rates and cause-of-death data are summarized in Table 5 and compared in Table 6. Based

Table 3 – Complications of surgery in eligible patients

	Without lymph-node dissection (n = 370)		With complete lymph node dissection (n = 362)	
	n	%	n	%
Bleeding >1 l	24	6.5	34	9.4
Pleural damage	19	5.1	16	4.4
Infection	21	5.7	19	5.2
Bowel damage	5	1.4	2	0.6
Embolism	4	1.1	8	2.2
Lymph fluid drainage	9	2.4	14	3.9
Total	82		93	

Table 4 – Pathological tumor characteristics

	Without lymph-node dissection		With complete lymph-node dissection	
	n	%	n	%
pT category				
T0	5	1	4	1
T1	19	5	21	6
T2	230	65	221	63
T3	96	27	101	29
T4	2	1	3	1
TX	2	1	3	1
pN-category				
N0	–	–	332	96
N1	–	–	5	1
N2	–	–	6	2
N3	–	–	3	1
Grade				
G0	11	3	11	3
G1	98	28	78	22
G2	152	44	156	45
G3	49	14	67	19
G4	2	1	2	1
GX	37	11	34	10

Table 5 – Cause of death

Cause of death	Without lymph-node dissection (n = 389)	With complete lymph node dissection (n = 383)
Alive	254 (65%)	246 (64%)
Malignant disease	67 (17%)	68 (18%)
CVD	28 (7%)	29 (8%)
Other/unknown	40 (10%)	40 (10%)

CVD = cardiovascular disease.

on a median follow-up period of 12.6 yr and a maximum follow-up period of 17.2 yr, 272 patients died, 135 (35%) in the group without lymph-node dissection and 137 (36%) in the group of patients who underwent a complete lymph-node dissection ($p = 0.87$). The median duration of survival in both groups was 15 yr (Fig. 1). Overall, 135 (17.5%) patients died from renal cancer, 67 patients in the group without lymph-node dissection and 68 patients in

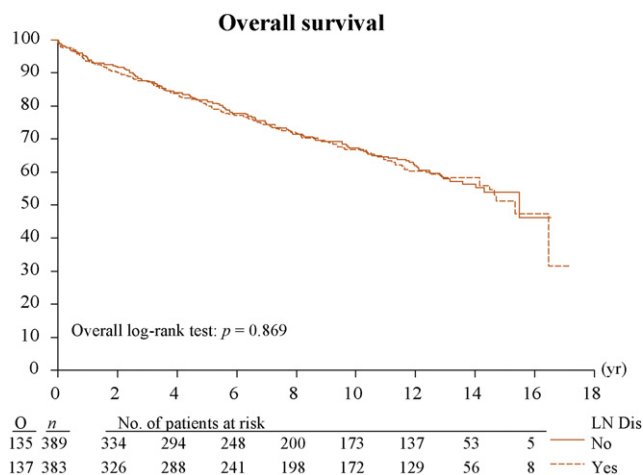


Fig. 1 – Overall duration of survival. O: number of deaths; n: total number of patients; LN Dis: lymph node dissection.

the group underwent a complete lymph-node dissection.

Figs. 2 and 3, respectively, show the time to progression and the duration of progression-free survival by treatment group. As can be seen in Table 6, there are no significant differences between the two treatment groups for any of the end points considered.

4. Discussion

Until now, the benefit of lymph-node dissection in conjunction with a radical nephrectomy on prognosis has remained controversial. Several studies attempting to solve this controversy have been published, but none of them were set up as prospective randomized trials. Moreover, as was discussed in our previous paper [13], the results of these studies were sometimes conflicting, probably due to patient selection, differences in staging techniques, and variations in the extent of lymph-adenectomy.

In several urologic and nonurologic tumors a complete lymph-node dissection seems to improve

Table 6 – Comparison of end points

	Without lymph-node dissection (n = 389)	With complete lymph-node dissection (n = 383)	Hazard ratio	95% confidence interval	p value
Death	135 (35%)	137 (36%)	1.02	0.80–1.29	0.87
Local regional progression	34 (9%)	26 (7%)	0.77	0.46–1.28	0.31
Distant progression	58 (15%)	60 (16%)	1.05	0.73–1.50	0.81
Local or distant progression	93 (24%)	87 (23%)	0.95	0.71–1.27	0.70
Progression or death	156 (40%)	159 (42%)	1.02	0.82–1.28	0.84
Second primary	45 (12%)	36 (9%)	0.79	0.51–1.22	0.28

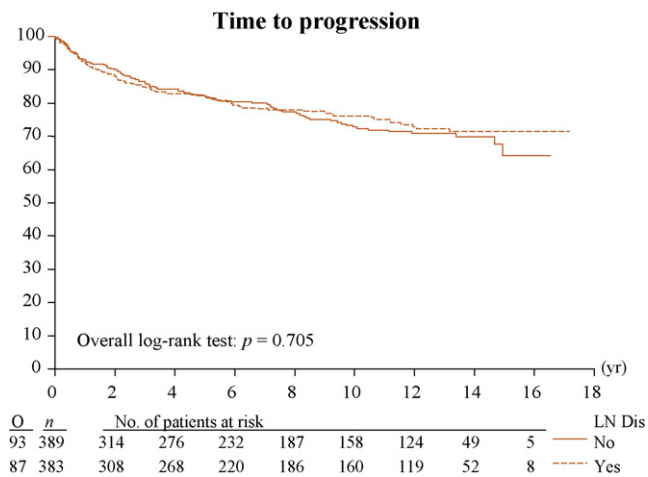


Fig. 2 – Time to progression of disease. O: number of patients with progression of disease; n: total number of patients; LN Dis: lymph node dissection.

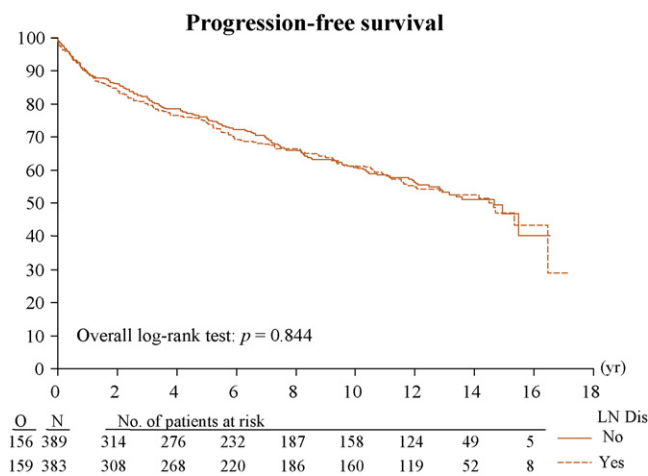


Fig. 3 – Duration of progression-free survival. O: number of patients who died; N: the total number of patients; LN Dis: lymph node dissection.

survival. For decades, it has been a well-known fact that lymphadenectomy can be curative in testicular cancer. In other urologic malignancies lymph-node dissection may also improve survival. Stein and Skinner [16] concluded that there is growing evidence that an extensive lymph-node dissection may provide a survival advantage in patients with node-negative and node-positive bladder cancer. Even in urothelial cancer of the upper urinary tract, regional lymphadenectomy seems to offer survival benefits to selected groups of patients [17]. Joslyn and Konety [18] concluded from a retrospective review of the Surveillance, Epidemiology, and End Results (SEER) database that even in prostate cancer patients a more extensive lymph-node dissection could reduce the risk of prostate cancer-specific death.

In 1990 Giuliani et al [19] reported their experience with 200 consecutive radical nephrectomies with extensive lymphadenectomy. For the patients with N+ disease, they found an intermediate survival between the patients with tumors confined to the kidney and those with metastatic disease, suggesting a therapeutic benefit of lymphadenectomy. However, Siminovitch et al [20], Giberti et al [9], and Minervini et al [24] found a complete lymph-node dissection to be of no therapeutic value. Pizzocaro and Piva [8] estimated the survival advantage of a complete lymph-node dissection adjunct to a radical nephrectomy to be only about 6% at best. They concluded that the surgical procedure was safe enough to justify a lymph-node dissection, but that a very large number of patients would be necessary to demonstrate any benefit from the procedure. Schafhauser et al [25] retrospectively studied 1035 patients with renal-cell cancer who were operated upon with curative intent. Of those 1035 patients, 531 patients underwent a radical nephrectomy with a systematic lymphadenectomy. The majority of these patients were shown to have pN0 disease. Among the patients with pN1–3 disease, only 20 patients survived for >5 yr. So, out of 531 patients only 20 patients (4%) had an advantage from the lymph-node dissection in conjunction with the radical nephrectomy. Despite this low number, they advocated performing a systematic lymphadenectomy together with the radical nephrectomy, because other curative modalities are currently lacking, and a lymphadenectomy does not increase the morbidity of the surgical procedure.

Joslyn et al [21] retrospectively studied 4453 patients from the SEER database who had undergone radical nephrectomy for renal-cell cancer. In 1558 of these patients at least one lymph node had been examined after lymph node removal. They studied the number of nodes removed during surgery and the nodal burden (the ratio of the number of positive nodes to the number of nodes examined). They found an inverse correlation between the number of positive nodes and cancer-specific survival. However, they found no significant association between the number of nodes examined and cancer-specific survival. Apparently the number of nodes removed did not have an impact on survival.

Pantuck et al [22] retrospectively studied 900 patients who underwent radical nephrectomy for renal cancer. They divided these patients in four pathologic groups: those without metastases, those with only regional lymph-node enlargement, those with only distant metastases, and those with both

enlarged regional lymph nodes and distant metastases. These groups were subdivided into cohorts that did and did not undergo retroperitoneal lymph-node dissection at nephrectomy. This study showed that there was no survival benefit for those patients without enlarged lymph nodes at diagnosis who underwent a lymph-node dissection compared with the patients without enlarged nodes who did not have a lymphadenectomy. However, they found a statistically significant survival advantage in 112 patients with node-positive disease who underwent lymph-node dissection together with nephrectomy compared with 17 who did not undergo lymph-node dissection. Similar findings were made by Giberti et al [9], who found a 53% 5-yr survival rate in patients with pN+M0V0 disease who underwent radical nephrectomy together with a lymph-node dissection. These findings support our data that, in node-negative disease, lymph-node dissection has no apparent therapeutic advantage.

Canfield et al [23] reported on 40 patients with node-positive renal-cell cancer without distant metastases. They found that patients with only one positive node survived significantly longer than patients with more than one positive node (median: 35.7 mo vs 14.5 mo). They found in this observation an argument to perform a complete resection of all nodal disease.

The low rate of nodal metastases seen in the present study might have several causes: First, it may be possible that the preoperative staging was adequate and very specific (net predictive value [NPV] = 96%). Second, in this study stepwise pathologic evaluation of the lymph nodes was not done. It might be possible that, if stepwise pathologic examination of the lymph nodes had been performed, more lymph-node metastases would have been found. Third, changes in patient populations may be the reason for the low number of metastases. With the frequent use of ultrasonography, more small tumors may have been detected than were detected previously, resulting in less cases of metastatic disease.

In 84 patients there were palpably enlarged lymph nodes detected during surgery. In only 14 of these 84 patients (17%) tumor was found in these lymph nodes. That means that in many cases the enlargement was not due to metastasis. Renal cancer is not conclusively metastatic based on enlargement of lymph nodes alone. To be certain, fine-needle aspiration of the enlarged node for cytological evaluation must be done prior to operation. Similar observations were made by Studer et al [26].

5. Conclusions

In summary, this study does show that lymph-node dissection combined with a radical nephrectomy does not increase morbidity or mortality, but its efficacy in terms of prolonged survival or progression-free survival could not be demonstrated. This is mainly due to the low number of lymph-node metastases detected by lymphadenectomy. This does not mean that a lymph-node dissection should be completely abandoned. In individual cases, for instance in cases of aggressive cancer, a patient may benefit from a lymph-node dissection. It will, however, be difficult to identify those individual patients.

Author contributions: Jan Blom had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Blom, Schroeder, Sylvester.

Acquisition of data: Blom, van Poppel, Jacqmin, Marechal, De Prijck.

Analysis and interpretation of data: Sylvester, Blom, van Poppel.

Drafting of the manuscript: Blom, Sylvester.

Critical revision of the manuscript for important intellectual content: Sylvester, van Poppel.

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References

- [1] Thrasher JB, Paulson DF. Prognostic factors in renal cancer. *Urol Clin N Am* 1993;20:247–62.
- [2] Campbell SC, Novick AC, Bukowski RM. Renal tumors. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. *Campbell-Walsh Urology*. Philadelphia, PA: Saunders; 2007. p. 1567–637.
- [3] Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *J Urol* 1969;101:297–301.
- [4] Hultèn L, Rosencrantz M, Seeman T, Wahlqvist L, Ahrén C. Occurrence and localization of lymph node metastases in renal carcinoma. *Scand J Urol Nephrol* 1969;3:129–30.
- [5] Angervall L, Wahlqvist L. Follow-up and prognosis of renal carcinoma in a series operated by perifascial nephrectomy with adrenalectomy and retroperitoneal lymphadenectomy. *Eur Urol* 1978;4:13–7.
- [6] Waters WB, Richie JP. Aggressive surgical approach to renal cell carcinoma: review of 130 cases. *J Urol* 1979;122:306–9.
- [7] Petkovic S. The value of tumor tissue penetration into the renal veins and lymph nodes as anatomical classification and kidney tumor prognostic parameters. *Eur Urol* 1980;6:289–92.
- [8] Pizzocaro G, Piva L. Pros and cons of retroperitoneal lymphadenectomy in operable renal cell carcinoma. *Eur Urol* 1990;18(Suppl 2):22–3.
- [9] Giberti C, Oneto F, Martorana G, Rovida S, Carmignani G. Radical nephrectomy for renal cell carcinoma: long-term results and prognostic factors on a series of 328 cases. *Eur Urol* 1997;31:40–8.
- [10] Herrlinger A, Schrott KM, Sigel A, Giedl J. Results of 381 transabdominal radical nephrectomies for renal cell carcinoma with partial and complete en bloc lymph-node dissection. *World J Urol* 1984;2:114–21.
- [11] Giuliani L, Martorana G, Giberti C, Pescatore D, Magnani G. Results of radical nephrectomy with extensive lymphadenectomy for renal cell carcinoma. *J Urol* 1983;130:664–8.
- [12] Robson CJ. Radical nephrectomy for renal cell carcinoma. *J Urol* 1963;89:37–42.
- [13] Blom JHM, van Poppel H, Marechal JM, et al. Radical nephrectomy with and without lymph node dissection: preliminary results of the EORTC randomized phase III protocol 30881. *Eur Urol* 1999;36:570–5.
- [14] McDonald MW. Current therapy for renal cell carcinoma. *J Urol* 1982;127:211–7.
- [15] Harmer MH, ed. *TNM-classification of malignant tumours*. Geneva, Switzerland: UICC, International Union Against Cancer; 1978.
- [16] Stein JP, Skinner DG. The role of lymphadenectomy in high-grade invasive bladder cancer. *Urol Clin N Am* 2005;32:187–97.
- [17] Kondo T, Nakazawa H, Ito F, Hashimoto Y, Toma H, Tanabe K. Impact of the extent of regional lymphadenectomy on the survival of patients with urothelial carcinoma of the upper urinary tract. *J Urol* 2007;178:1212–7.
- [18] Joslyn SA, Konety BR. Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. *Urology* 2006;68:121–5.
- [19] Guiliani L, Giberti C, Martorana G, Rovida S. Radical extensive surgery for renal cell carcinoma: long-term results and prognostic factors. *J Urol* 1990;143:468–77.
- [20] Siminovitch JP, Montie JE, Straffon RA. Lymphadenectomy in renal adenocarcinoma. *J Urol* 1982;127:1090–1.
- [21] Joslyn SA, Sirintrapun SJ, Konety BR. Impact of lymphadenectomy and nodal burden in renal cell carcinoma: retrospective analysis of the national surveillance, epidemiology, and end results database. *Urology* 2005;65:675–80.
- [22] Pantuck AJ, Zisman A, Dorey F, et al. Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. *J Urol* 2003;169:2076–83.
- [23] Canfield SE, Kamat AM, Sánchez-Ortiz RF, Detry M, Swanson DA, Wood CG. Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease (clinical stage TxN1–2M0): the impact of aggressive surgical resection on patient outcome. *J Urol* 2006;175:864–9.
- [24] Minervini A, Lilas L, Morelli G, et al. Regional lymph node dissection in the treatment of renal cell carcinoma: is it useful in patients with no suspected adenopathy before or during surgery? *BJU Int* 2001;88:169–72.
- [25] Schafhauser W, Ebert A, Brod J, Petsch S, Schrott KM. Lymph node involvement in renal cell carcinoma and survival chance by systematic lymphadenectomy. *Anticancer Res* 1999;19:1573–8.
- [26] Studer UE, Scherz S, Scheidegger J, et al. Enlargement of regional lymph nodes in renal cell carcinoma is often not due to metastases. *J Urol* 1999;144:243–5.