



Main Determinants of the Extent of Lymphadenectomy in Radical Cystectomy: A Study Based on Clinical Practice

Principais Preditores da Extensão da Linfadenectomia na Cistectomia Radical: Um Estudo Baseado na Prática Clínica

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Abstract

Introduction: During radical cystectomy of patients with muscle-invasive bladder cancer, pelvic lymphadenectomy is used not only for an accurate staging, but also to provide local and regional control of the disease. Although recent studies evaluating the anatomical extent of lymphadenectomy recommend an extended template, the relation between the extent of lymphadenectomy and the number of dissected nodes remains controversial.

The aim of this study was to determine the main predictors of the extent of lymphadenectomy in patients with bladder cancer submitted to radical cystectomy.

Material and Methods: Retrospective analysis of 119 patients with muscle-invasive or selected high-risk non-muscle invasive bladder cancer submitted to radical cystectomy between 2010 and 2015 at our institution.

Results: Standard and extended lymphadenectomy was performed in 87 and 22 patients, respectively. Extended template was statistically associated with a higher number of lymph nodes dissected when compared to standard lymphadenectomy, (14 vs 11 lymph nodes; $p < 0.05$) and showed a trend toward better overall survival, although without statistical significance (HR = 0.52, 95% CI 0.23-1.21). Extended lymphadenectomy was performed preferentially in patients undergoing an orthotopic bladder substitution (47.8%) relatively to other types of urinary diversion (around 10% - 11%). These patients had more lymph nodes dissected relatively to cutaneous ureterostomy (15 vs 8 lymph nodes), on average. **Conclusion:** The surgeon's decision about the type of urinary diversion to be performed is the main determinant of the extent of lymphadenectomy in patients with bladder cancer undergoing radical cystectomy. The number of retrieved lymph nodes was associated with the extent of lymphadenectomy and with a trend toward better overall survival.

Keywords: Cystectomy; Lymph Node Excision; Urinary Bladder Neoplasms; Urinary Diversion

Resumo

Introdução: Durante a cistectomia radical de doentes com neoplasia vesical musculo-invasiva, a linfadenectomia pélvica é usada não apenas para um estadiamento preciso, mas também para controlo local e regional da doença. Apesar de estudos recentes recomendarem a realização de uma linfadenectomia extensa, a relação entre a extensão da linfadenectomia e o número de gânglios ressecados permanece controverso.

O objectivo do estudo foi determinar os principais preditores da extensão da linfadenectomia em pacientes com neoplasia vesical submetidos à cistectomia radical.

Material e Métodos: Análise retrospectiva de 119 doentes com neoplasia vesical musculo-invasiva ou não-invasiva de alto risco submetidos a cistectomia radical entre 2010 e 2015 na nossa instituição.

Resultados: A linfadenectomia padrão e extensa foram realizadas em 87 e 22 doentes, respetivamente. A linfadenectomia extensa demonstrou um número estatisticamente superior de gânglios removidos relativamente à linfadenectomia padrão (14 vs 11 gânglios, $p < 0,05$) e ainda uma tendência para uma maior sobrevida global, embora sem significância estatística (HR=0,52, 95% CI 0,23-1,21). A linfadenectomia extensa foi realizada preferencialmente em pacientes submetidos a substituição ortotópica da bexiga (47,8%) relativamente a outros tipos de derivação urinária (cerca de 10% - 11%). Em média, esses doentes tiveram mais gânglios removidos durante a linfadenectomia do que os doentes submetidos a ureterostomia cutânea (15 vs 8 gânglios).

Conclusão: A decisão do cirurgião quanto ao tipo de derivação urinária a ser realizada é o principal preditor da extensão da linfadenectomia em pacientes com neoplasia da bexiga submetidos à cistectomia radical. O número de gânglios removidos associou-se à extensão da linfadenectomia, com tendência para uma maior sobrevida global.

Palavras-chave: Cistectomia; Derivação Urinária; Excisão de Gânglio; Neoplasias da Bexiga Urinária

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Introduction

Radical cystectomy (RC) with bilateral lymphadenectomy (LND) is the gold standard treatment for selected high risk non-muscle-invasive bladder cancer and, mainly, those with muscle-invasive disease. However, approximately 50% of patients develop metastasis and die from their disease within 5 years after the surgery.¹

Nodal disease is a powerful predictor of cancer-specific survival and a significant determinant of the therapeutic course following surgery.^{2,6} At RC, nearly 25% of patients already have lymph node metastasis, especially the higher histopathological stages.^{3,7,8}

During cystectomy, lymphadenectomy is used not only for an accurate staging, but also to provide local and regional control of the disease, increasing long-term survival⁵⁻¹² and even curing up to 30% of patients with limited disease without any adjuvant therapy.^{2,4,13-16}

Although recent studies evaluating the extent of LND recommend an extended one, at least up to common iliac vessels, the extent of lymphadenectomy and its relation with the number of nodes dissected remains on discussion.²

The aim of this study was to find the main determinants of the extent of lymphadenectomy in patients with bladder cancer submitted to radical cystectomy.

Material and Methods

From January 2010 until December 2015 all patients with bladder cancer treated with radical cystectomy at our institution were reviewed. The indications for RC with LND included muscle invasive bladder carcinoma and carcinoma *in situ* refractory to treatment with transurethral resection combined with intravesical chemotherapy. Standard (pelvic) LND was anatomically defined by the pelvic region that included external iliac, hypogastric, obturator and deep obturator lymph nodes, until the bifurcation of common iliac vein or the origin of external iliac vein. Extended LND was defined by the territory of standard plus common iliac, presacral and presciatic nodes, limited superiorly by the bifurcation of abdominal aortic artery or the origin of common iliac vein.

Socio-demographic, clinical and histopathological characteristics were analyzed using hospital databases, consulted for the last time in January of 2016. Charlson Comorbidity Scoring System adjusted to age was used to characterize patients. The histopathological classification, based on the 7th edition of the AJCC Cancer Staging Manual TNM cancer staging system, and the number of lymph nodes removed were acquired from the histopathology report.

Correlations between the surgeon's perception of extent of LND and the number of nodes dissected were assessed by using chi-squared test. The level of significance was set at $p < 0.05$. Overall free-survival (OS) was evaluated from the

date of surgery to time of death using Kaplan-Meier curves and Cox-regression analysis.

Results

The sample was composed by 119 patients, 91 males (76.5%) and 28 females (23.5%) submitted to radical cystectomy. The mean age was 67 years-old and the majority had a low age-adjusted Charlson Comorbidity index (median=5, 25th percentile: 3; 75th percentile: 7). Urothelial carcinoma was the most common type of bladder cancer ($n = 97$; $p = 81.5\%$) followed by squamous cell carcinoma ($n = 11$; $p = 9.2\%$), carcinoma *in situ* ($n = 5$; $p = 4.2\%$) and other types ($n = 6$; $p = 5.0\%$). Lymph node metastasis were found in 36 patients (N1+N2, $p = 30.3\%$). Adjuvant chemotherapy was given to 29 patients of this group, and neoadjuvant chemotherapy was given to 12 patients (see Table 1).

According to surgical reports, the majority of patients received a cutaneous ureteroileostomy/Bricker ileal conduit (IC) ($n = 68$, $p = 57.1\%$), followed by cutaneous ureterostomy ($n = 28$, $p = 23.5\%$) and, less frequently, by orthotopic bladder substitution (OBS) ($n = 23$, $p = 19.3\%$).

One hundred and nine patients were submitted to lymphadenectomy. A standard procedure was performed in 87 (79.8%) and only 22 had an extended lymphadenectomy (20.2%) (Table 2).

When a standard LND was performed, a mean of 11 nodes was retrieved whereas a mean of 14 lymph nodes was retrieved when an extended LDN was performed. The inferior value of the standard LDN compared to the extended LND showed statistical significance ($p = 0.04$) as it can be seen in Fig. 1.

From the group of patients undergoing cutaneous ureterostomy ($n = 28$), a standard lymphadenectomy was performed in 53.6% ($n = 15$) and an extended LND in 10.7% ($n = 3$). The remaining 10 individuals did not undergo lymphadenectomy. From the group of patients undergoing IC ($n = 68$), a standard LND was performed in 88.2% ($n = 60$) and an extended LND in 11.8% ($n = 8$). From the group of patients undergoing OBS ($n = 23$), a standard lymphadenectomy was performed in 52.2% ($n = 12$) and an extended lymphadenectomy in 47.8% ($n = 11$).

From the group of patients in whom a standard LND was performed ($n = 87$), 69.0% ended up undergoing a IC ($n = 60$), 17.2% a cutaneous ureterostomy ($n = 15$) and 13.8% a OBS ($n = 12$). From the group of patients in whom an extended LND was performed ($n = 22$), 13.6% ended up undergoing a IC ($n = 3$), 36.4% a cutaneous ureterostomy ($n = 8$) and 50.0% a OBS ($n = 11$).

The mean numbers of removed lymph nodes in patients undergoing cutaneous ureterostomy, IC and OBS were 7.8, 12.1 and 15.0, respectively.



Table 1: Sample descriptive data

Age		Tis	5 (4.2%)
Mean	67 (59.8 - 75.0)	T0	2 (1.7%)
Gender		T1	24 (20.2%)
Male	91 (76.5%)	T2	19 (16.0%)
Female	28 (23.5%)	T3	41 (34.5%)
Age Adjusted Charlson Index		T4	27 (22.7%)
1	1 (0.8%)	Ta	1 (0.8%)
2	22 (18.5%)	N0	73 (61.3%)
3	13 (10.9%)	N1	15 (12.6%)
4	16 (13.5%)	N2	21 (17.7%)
5	12 (10.1%)	No LND	10 (8.4%)
6	15 (12.6%)	Pathologic Analysis	
7	11 (9.2%)	Squamous Cell Ca.	11 (9.2%)
8	8 (6.7%)	Urothelial Ca. †	97 (81.5%)
9	6 (5.0%)	CIS	5 (4.2%)
10	11 (9.2%)	Others ‡	6 (5.0%)
11	4 (3.4%)		

Age: mean (25th percentile - 75th percentile). Ta: noninvasive papillary carcinoma. Tis: carcinoma *in situ*. †urothelial: urothelial low or high degree, mixed urothelial cancer, urothelial papilar cancer and sarcomeric neoplasia. ‡others: colorectal adenocarcinoma, papillary adenocarcinoma, giant paragangliomas, small B-cells lymphoma or sarcoma.

Although age, gender and the template of lymphadenectomy were not significantly associated with overall survival, the type of urinary diversion, namely cutaneous ureterostomy, was associated with an increased risk of death (HR = 2.14, 95% CI 1.05-4.37). However, when including Charlson Comorbidity index in the multivariate analyses model, cutaneous ureterostomy loses its statistically significance and the only parameter that was associated with an increased risk of death was the Charlson Comorbidity index (HR = 1.14, 95% CI 1.02-1.28).

At 20 months of follow-up, there is difference between extended and standard LND: patients in whom extended lymphadenectomy was performed had a survival > 75%, against < 50% of patients in whom standard lymphadenectomy was performed, as it can be seen in Fig. 2.

Discussion and Conclusion

According to the European Association of Urology (EAU) guideline recommendations, lymph node staging should be performed in every patient prior to RC.¹⁷ However, current imaging techniques (computed tomography and magnetic resonance imaging) do not detect every LN metastases.¹⁸

In clinical practice, the extent of LND performed has been based on patient factors such as preoperative staging, health status and tumor features. Moreover, surgeon's expertise deciding the better anatomic template for each patient should be considered a non-neglected matter in this issue.¹⁴ Unfortunately, only limited data are available regarding the determinants of surgeon's decision.

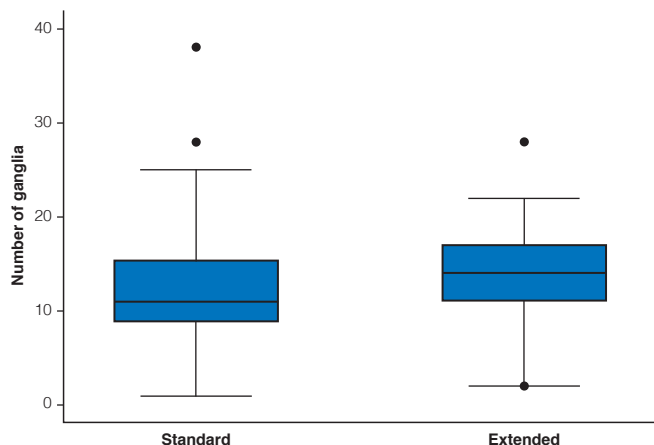
Table 2: Surgical descriptive data

Lymphadenectomy	
Standard	87 (79.8%)
Extended	22 (20.2%)
Type of Derivation	
OBS	23 (19.3%)
IC	68 (57.1%)
Cutaneous Ureterostomy	28 (23.5%)
Chemotherapy	
Neoadjuvant	12 (10.1%)
Adjuvant	29 (24.4%)

A total of 119 patients were submitted to radical cystectomy. From these, only 109 patients were submitted to a radical cystectomy with lymph node dissection.

OBS: orthotopic bladder substitution; IC: cutaneous ureterostomy or Bricker ileal conduit.

Lymph node count has been used as a surrogate of the extent of lymphadenectomy and its therapeutic effect.¹¹ Previously, Whitmore and Marshall described an adequate LND based on an anatomic template.¹⁹ However, not even an extended LND assures total accuracy with regard to nodal status.¹⁴ In fact, in an analysis of a large prospective database, Koppie *et al* reported that the probability of survival continues to rise as the number of lymph node removed increases and found no evidence supporting the definition of a minimum number of lymph nodes for optimizing BC survival.^{6,20} They also reported that older and sicker patients are less likely to have an LND and if they do so, they are more likely to have fewer lymph nodes removed.^{6,20} In a review of surgeon's practice patterns in the

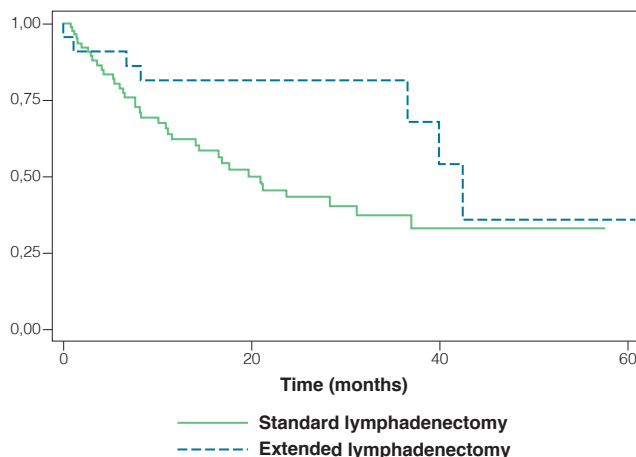


Comparison between the number of lymph nodes dissected and the surgeon perception of type of lymphadenectomy: standard lymphadenectomy (left) and extended lymphadenectomy (right). $p < 0.05$.

Figure 1: Comparison between number of ganglia and surgeon perception of type of lymphadenectomy.

Surveillance, Epidemiology, and End Results (SEER) database, Koney and Joslyn demonstrated that there was a wide distribution in the number of lymph nodes examined when RC was performed.²¹ This observation parallels single-center reports where there is a significant variability in the mean number of lymph nodes evaluated ranging from 8 to 30.²²⁻²⁴ Some surgeons remove only the common iliac nodes, whereas others perform an extensive dissection that includes the iliac vessels and the aortic bifurcation.⁶ Moreover, besides the anatomical extent and the thoroughness of the dissection, the number of reported lymph nodes is also largely dependent on the type of packing and processing.^{8,20,21,25-27} Other studies have shown that patient's characteristics such as age, BMI, clinical tumor stage, type of tumor growth, multifocality and surgical margins could also substantially influence the total nodal and even could have some impact on the surgeon's decisions.^{8,9,26}

In our study, the mean number of lymph nodes removed from patients submitted to a radical cystectomy with lymphadenectomy was 12. Although the number of retrieved nodes in the standard LDN was inferior to the number of nodes in the extended LND with statistical significance ($p = 0.04$), it is questionable if this difference is clinically relevant. The anatomical template of the lymphadenectomy differed with the type of urinary diversion applied. When a cutaneous ureterostomy or IC was performed, only 18% and 12% of the patients, respectively, were submitted to an extended LND, whereas almost 50% of the patients in the OBS group were submitted to an extended LND. In fact, the type of diversion showed differences in the mean number of lymph nodes retrieved, with a mean of 8 lymph nodes removed in a cutaneous ureterostomy and a mean of 12 and 15 lymph nodes removed when a IC or OBS was performed, respectively.



Overall survival analysis comparing extended vs standard lymphadenectomy at radical cystectomy.

Figure 2: 5-year survival analysis by extent of lymphadenectomy.

Table 3: Predictors of mortality

Variable	HR	95% CI
Age	1.03	0.99 - 1.07
Gender		
Female	1.41	0.69 - 2.90
Male	Ref	
Charlson Comorbidity Score	1.14	1.02 - 1.28
Urinary diversion		
Cutaneous Ureterostomy	1.55	0.71 - 3.35
Orthotopic Bladder Substitution	1.21	0.54 - 2
Bricker Ileal Conduit	Ref	
Lymphadenectomy template		
Extended	0.52	0.23 - 1.21
Standard	Ref	

Cox regression analysis with Breslow method with ties.
CI: confidence interval. HR: hazard ratio.

The type of urinary diversion was also a major predictor of survival with a greater risk of death for patients submitted to a cutaneous ureterostomy although its significance was lost to the Charlson Comorbidity Score when this parameter was included in the multivariate analysis.

At 20 months of follow-up, the lymphadenectomy template had different results with a survival of more than 75% for patients submitted to an extended lymphadenectomy and a survival of less than 50% for patients submitted to a standard lymphadenectomy.

This study showed that patients with greater comorbidities had a higher probability of undergoing a cutaneous ureterostomy, associated with fewer removed LN and inferior overall sur-



vival. In fact, patients' comorbidities were a major determinant in surgeon's decision about the type of urinary diversion and the extent of lymphadenectomy was very dependent on the type of urinary diversion.

In conclusion, it seems that the surgeon's decision about the type of urinary diversion to be performed in patients with bladder cancer undergoing radical cystectomy is the main determinant of the extent of lymphadenectomy, with a direct impact on the number of removed LN and probably on survival. ●

Ethical Disclosures

Conflicts of Interest: The authors report no conflict of interest.

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Responsabilidades Éticas

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