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Variability in surgical quality in a phase III clinical trial of radical cystectomy in patients with organ-confined, node-negative urothelial carcinoma of the bladder

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Abstract

Background and Objectives—Previous studies have shown that variability in surgical technique can affect the outcomes of cooperative group trials. We analyzed measures of surgical quality and clinical outcomes in patients enrolled in the p53-MVAC trial.

Methods—We performed a *post-hoc* analysis of patients with pT1-T2N0M0 urothelial carcinoma of the bladder following radical cystectomy (RC) and bilateral pelvic and iliac lymphadenectomy (LND). Measures of surgical quality were examined for associations with time to recurrence (TTR) and overall survival (OS).

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Results—We reviewed operative and/or pathology reports for 440 patients from 35 sites. We found that only 31% of patients met all suggested trial eligibility criteria of having 15 lymph nodes identified in the pathologic specimen (LN#) and having undergone both extended and presacral LND. There was no association between extent of LND, LN#, or presacral LND and TTR or OS after adjustment for confounders and multiple testing.

Conclusions—We demonstrated that there was substantial variability in surgical technique within a cooperative group trial. Despite explicit entry criteria, many patients did not undergo per-protocol LNDs. While outcomes were not apparently affected, it is nonetheless evident that careful attention to study design and quality monitoring will be critical to successful future trials.

Keywords

Carcinoma; transitional cell; chemotherapy; adjuvant; cystectomy; genes; p53

INTRODUCTION

The p53-MVAC trial (SWOG 4B951/NCT00005047) reported that p53 overexpression was not associated with time to recurrence (TTR) or overall survival (OS) in patients with organ-confined, node-negative urothelial carcinoma of the bladder (UCB) treated with radical cystectomy (RC) and bilateral pelvic and iliac lymphadenectomy (LND) [1]. Among patients with p53-positive tumors, adjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) did not improve cancer-specific survival more than RC alone.

In an attempt to overcome surgical confounders a standard anatomic template and suggested minimum lymph-node yield (LN#) for the bilateral LND were requested by the p53-MVAC trial protocol. Meticulous LND at the time of RC in muscle-invasive UCB improves loco-regional control and may be associated with long-term cancer control in patients with pathologic metastasis [2,3]. While the removal of between 13 to 25 nodes has been proposed as a metric of RC quality assurance in order to identify the greatest number of patients with pathologically proven nodal metastases, this range has not been defined prospectively [4,5]. The level of evidence in support of an appropriate extent of LND during RC lags behind that of the available data for other organ sites [6,7].

It was our intention to determine whether the measures of surgical quality defined in the p53-MVAC trial protocol had been met by the participating institutions. We investigated the degree to which the surgeons adhered to the protocol and whether any variation in surgical technique affected clinical outcomes. Below we present a *post-hoc* analysis of variability in these measures of surgical quality along with their associations with TTR and OS in patients with organ-confined, node-negative UCB in the trial.

MATERIALS AND METHODS

Patients and Interventions

Methods of the p53-MVAC trial were previously reported [1,8]. In brief, patients with stage pT1-T2N0M0 UCB who had undergone RC and bilateral pelvic and iliac LND within the

preceding nine weeks were eligible. Patients with pT0, pTa, or pTis disease were included if cT1, cT2a, or cT2b disease was present on the pre-RC transurethral resection specimen. Patients were required to have 15 LNs identified on pathology or a normal post-operative abdominal/pelvic computed tomography (CT) scan if fewer were identified. Patients with a history of prior pelvic radiotherapy were excluded. Per-protocol bilateral pelvic and iliac LND was an extended LND initiated at or above the aortic bifurcation including the bilateral common, external, and internal iliac LNs and the presacral and obturator LNs. Patients with positive surgical margins were excluded. Those with p53-positive immunohistochemistry (10% nuclear immunoreactivity) were randomly chosen to receive adjuvant MVAC or to be observed. Follow-up evaluations occurred every three months for the first year, every six months for the following four years, and annually thereafter. Patients who refused to be randomized within the trial were observed. Because no differences were observed between patients in the two randomized arms of the study, all patients were combined for this analysis.

Surgical Quality Study

Pathology reports were reviewed and each of the anatomic LN specimens was recorded with respect to the number of nodes identified by the pathologist in order to determine the LN#, the extent of LND based on the most proximal node packets submitted, and whether or not presacral LND had been performed. Extent of LND was defined as standard (below the common iliac bifurcation) or extended (common iliac and above, up to aortic bifurcation as the proximal extent). The extent of LND actually performed on the patients was determined on the basis of a re-review of operative and pathology reports. While the majority of patients were enrolled in centers experienced in RC and specimens were reviewed by genitourinary pathologists, there was no protocol-specified submission of node packets nor was there a standardized methodology for pathologic evaluation. Differences in sample medians were assessed using the unpaired Mann–Whitney–Wilcoxon test or the Kruskal-Wallis one-way analysis of variance test. Differences among categorical variables were assessed using Pearson's Chi-squared test with Yates's continuity correction. Surgical quality variables were examined in univariate and multivariate Cox proportional hazards models for associations with TTR and OS. TTR was the time from registration to the first observation of disease recurrence. Patients who died of unrelated causes were excluded. OS was the time from registration to time of death due to any cause. Reported *p* values were not adjusted for multiple testing.

RESULTS

Study Cohort

Five hundred and twenty-one patients from 39 sites were registered between August 1997 and January 2006. Of these, 499 were eligible for the study. An available subset of 440 operative and/or pathology reports from 35 sites was re-reviewed for this analysis. Demographic and pathologic variables for these 440 patients are summarized in Table 1. The median age at RC was 62 years (interquartile range [IQR]: 54 – 70).

Surgical Quality Variation

The median LN# for all patients was 19 (IQR: 12 – 35) (Table 2). Thirty-five percent of patients had <15 LNs identified in the pathologic specimen, 47% underwent extended LND, and 33% underwent presacral LND. Only 31% of patients concomitantly met all three suggested surgical quality metrics of having ≥15 LNs identified and undergoing both extended LND and presacral LND. Only 16% of patients who underwent extended LND had identification of <15 LNs, compared to 84% of those who underwent a true standard pelvic LND. Among this 16% of patients, 11 were from a single institution while the remaining 13 were distributed among eight institutions. The median LN# was 36 (IQR: 21 – 56) for patients who underwent extended LND compared to 14 (IQR: 10 – 19) for standard PLND ($p < 0.001$). The performance of presacral LND was associated with LND extent. Presacral LND was performed in 67% of patients who had an extended LND compared to 2% for standard PLND ($p < 0.001$). The median LN# for patients undergoing presacral LND was 46 (IQR: 32 – 65), significantly higher than the LN# of 14 (IQR: 10 – 19) in patients not undergoing presacral LND ($p < 0.001$). The manner in which extended LND and presacral LND are associated with higher LN# is further illustrated by the violin plots shown in Figure 1.

Temporal, Geographic, and Institutional Variation

The median LN# increased with time, from 17 (IQR: 10 – 28) in the first three years to 23 (IQR: 15 – 49) in the final three years of the study (Table 2). Unadjusted linear regression showed that for every passing year the LN# increased by 3.1 (95% confidence interval [CI]: 2.2 – 4.1). This time-dependent increase in LN# was primarily driven by increasing node counts at one institution at which 27% of all patients were treated. Adjustment of the linear regression model for institution abolished the observed univariate association between LN# and time. The percentage of patients with potentially suboptimal dissections in which <15 LNs were identified decreased with time, from 40% in the first three years to 23% in the final three years, with no statistically significant change in the extent of LND. Unlike the temporal trend for LN#, this trend was not obviously attributable to any individual institution.

Median LN# was associated with geography and was higher at U.S. than at non-U.S. sites (20 versus 11). U.S. sites were less likely to identify <15 LNs (30 versus 73%), more likely to perform extended LND (48 versus 37%), and more likely to perform presacral LND (37 versus 2%) than non-U.S. sites. These differences were almost entirely driven by two U.S. institutions. The median LN#s at these two sites were 48 (IQR: 34 – 73) and 29 (IQR: 19 – 37), respectively, and 15 (IQR: 10 – 19) at all other institutions as a group. Only 5 and 14% of patients at these two sites, respectively, had <15 LNs identified, compared to 51% of patients at all other institutions. Extended LND was performed in 92 and 76% of patients at these two sites, respectively, compared to only 23% of patients at other centers.

Survival Analyses

Five-year TTR and OS probabilities (previously reported [1] but recalculated for this subgroup of patients) were 0.78 (95% CI: 0.74 – 0.82) and 0.83 (95% CI: 0.79 – 0.87), respectively (Figure 2). There was no univariate association between year of RC, LN#, LND

extent, geography, or institution and TTR or OS (Figure 3). For sake of comparison, age at RC was associated with OS but not TTR in univariate analysis, while the known clinical predictor lymphovascular invasion (LVI) was significantly associated with both TTR and OS in univariate analysis. There was no association between year of RC, LN#, LND extent, presacral LND, geography, or institution and TTR or OS after adjustment for age, year, sex, race, institution, or study arm and adjustment for multiple testing. LVI, but not age at RC, remained significantly associated with both TTR and OS in multivariate analysis with adjustment for multiple testing.

DISCUSSION

The p53-MVAC trial primarily examined whether p53 overexpression had prognostic value for TTR and OS and predictive value for determining if patients with organ-confined, node-negative UCB treated with RC and bilateral pelvic and iliac LND would benefit from adjuvant MVAC chemotherapy. To the best of our knowledge, this was the first study in UCB to base a treatment decision on a molecular alteration and was, at the time, the largest randomized study of adjuvant chemotherapy. The original trial was based on the observation that p53 alterations identified UCB with a greater propensity to progress, but also those that would respond to cisplatin-containing chemotherapy [9,10]. The measures of surgical quality that we examined in this analysis were not summarized or considered as risk factors in the original study. The trial attempted to control for surgical confounders by specifying in the protocol a requirement for a bilateral pelvic and iliac template with a minimum LN# or a negative post-operative CT scan. We investigated the degree to which the surgeons actually adhered to the protocol and whether any variation in surgical technique affected clinical outcomes. We found marked variability in how RC was performed, especially with regards to the anatomic extent and completeness of the LND.

Our analysis revealed that only 31% of patients received the surgery suggested in the protocol, an extended LND including the presacral nodes with a LN# of 15. In many patients the LND was not initiated at the aortic bifurcation. The high proportion of per-protocol insufficient dissections may be explained by the fact that about half of the patients inappropriately underwent a standard rather than an extended LND, which was highly correlated with lower LN#. Another possible explanation is that surgeons were submitting specimens *en bloc* rather than in packets, a technique which has been shown to decrease LN# [11]. Technical variations in specimen processing by the pathologist, which we were unable to codify in this analysis, may also affect LN# [12]. Furthermore, the number of LNs identifiable in each patient may vary due to differences in anatomy [13]. The protocol inclusion criteria allowed the enrollment of patients with <15 LNs and a negative CT scan within nine weeks after RC, which may also have affected surgical quality.

Our analysis highlights the importance of minimizing surgical quality variability in clinical trials involving RC. Two institutions in this trial were responsible for the majority of protocol-compliant LNDs. These institutions likely did a better job of adhering to the surgical protocol because they were the centers at which the trial was based. Moreover, our data revealed the extent to which individual centers may introduce variability. The evident increase in LN# over time was largely driven by surgeons at a single institution. Possible

explanations include a more thorough surgical technique with time or modifications in pathologic specimen processing.

Because of the substantial variation in surgical quality in this trial, we performed a *post-hoc* analysis to determine if this variability was associated with clinical outcomes. Notably this involved a highly selected group of patients with pT1-T2N0M0 UCB. Among these patients, we detected no association between LN#, LND extent, or presacral LND and TTR or OS after controlling for multiple testing. Surgical quality measures were therefore not shown to have a major impact on outcome.

This finding is in contrast to a previous study by Herr *et al.* which examined the effect of surgical quality on UCB outcomes using data from the SWOG 8710 phase III neoadjuvant chemotherapy trial [14]. The patients in that trial differed in that they had cT2-T4aN0M0 disease and had undergone RC with or without LND. Among the univariate predictors of longer post-RC survival identified by Herr *et al.* were age <65 years, 10 LNs removed, and standard pelvic LND (versus none to limited LND). While within our data we also detected a univariate association between age at RC and OS, no significant associations between LN# and the extent of LND were identified. These discrepancies may be explained by the fact that patients in the SWOG 8710 trial had higher stage clinical disease at the time of RC, which may account for the detection of a protective effect with the removal of more LNs and performance of a more thorough LND.

Summary and Implications for Future Studies

One of our goals in undertaking this analysis was to highlight the challenges of managing adherence to protocols governing surgical quality in cooperative group trials. The p53-MVAC trial protocol pre-specified the need for a bilateral pelvic and iliac LND with a specific anatomic extent. Despite its stipulations, only 31% of patients received the complete suggested LND. At the time the trial was performed there was such a focus on randomization for adjuvant chemotherapy that surgical quality metrics for registration were perhaps not pursued as aggressively as they could have been. While the surgery was not the intervention being studied, variability in surgical quality between participating institutions may nonetheless introduce confounders that are difficult to detect, measure, or control. However, despite finding a marked lack of compliance with the surgical protocol in the p53-MVAC trial, we detected no independent associations between measures of surgical quality and clinical outcomes.

Our analysis emphasizes the importance of ensuring surgical quality control in multi-institutional clinical trials. The ongoing SWOG 1011 study (NCT01224665), which will contribute data on outcomes for T2-T4a with or without pathologic node-positive UCB, attempts to control for surgical quality variation. The trial explicitly spells out requirements for LND, involves real-time operative and pathologic monitoring, employs photo documentation, and involves rigorous surgeon and study-site credentialing prior to trial initiation at a particular site. These steps will help ensure that surgeons have sufficient experience and that hospitals have sufficient volume. Prospective sites must submit five cases up front to a peer-review committee. Our experience may help to improve trial design and highlights the challenges of clinical trial quality control.

Limitations

Our study is a secondary, *post-hoc* analysis of prospective trial data. Unmeasured variables may have contributed to the observed associations between measures of surgical quality and clinical outcomes. For example, the trial did not capture information on surgeon volume or experience. Regarding our LN# data, the myriad of factors that affect LN# has led some observers to question its utility as a marker of surgical quality, particularly for comparisons between institutions [15]. For this reason we also presented analyses of LND extent and presacral LND, which are thought to be more reliable. Last, the observed discrepancies in quality might also be attributable to protocol design limitations rather than to surgeons' inadequacy, although present.

CONCLUSIONS

While most patients did not meet all of the protocol-specified LND requirements, there was no independent association of LN#, LND extent, or presacral LND with TTR or OS in this organ-confined, node-negative UCB cohort. Multi-center trials should nonetheless incorporate quality controls to overcome potential confounders related to surgical protocols. Future prospective analyses with more accurate assessment tools are needed to better understand the role that surgical quality plays in oncological outcomes.

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ABBREVIATIONS AND ACRONYMS

CI	confidence interval
CT	computed tomography
EV	number of events
HR	hazard ratio
IQR	interquartile range
LCI	lower 95% CI
LN	lymph node
LN#	lymph-node yield
LND	lymphadenectomy
LVI	lymphovascular invasion

MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
OS	overall survival
RC	radical cystectomy
TTR	time to recurrence
UCB	urothelial carcinoma
UCI	upper 95% UCI

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Synopsis

There was substantial variability in surgical technique in the p53-MVAC trial. While trial outcome was not apparently affected, it is nonetheless evident that careful attention to study design and quality monitoring will be critical to successful future trials.

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Figure 1.

Violin plots of lymph node yield stratified by the extent of lymph node dissection and whether or not presacral lymphadenectomy was performed. Legend: The violin plot is a box plot with a rotated kernel density plot on each side. The plot allows the reader to visualize the median, interquartile range, range, and distribution of the data.

Figure 2.
Cumulative incidence of recurring (left) and overall survival (right).

Figure 3. Forest plots of time-to-recurrence and overall-survival hazard ratios with 95% confidence intervals from unadjusted Cox proportional hazards regression analyses.

Table 1

Patient demographic and clinical characteristics (n = 440).

Variable	No.	%
Age at cystectomy		
< 65 years	256	58
65 years	184	42
Gender		
Female	83	19
Male	357	81
Ethnicity		
White	399	91
Black	19	4
Hispanic	10	2
Asian	9	2
Hawaiian	2	<1
Native	1	<1
Pathologic stage		
pT1	232	53
pT2	208	47
Grade		
1	3	1
2	20	5
3	188	43
4	227	52
Missing	2	<1
Lymphovascular invasion		
Present	92	21
Absent	348	79

Table 2

Descriptive statistics of measures of surgical quality.

Variable	n	Median	IQR	p	% <15 LN	p	% Extended	p	% Presacral	p
All patients	440	19	12 - 35		35		47		33	
Year of cystectomy										
1997 - 1999	119	17	10 - 28	<0.001	40	0.002	47	0.73	35	0.29
2000 - 2002	176	18	13 - 33		40		46		30	
2003 - 2005	145	23	15 - 49		23		50		38	
Extent of lymph node dissection										
				<0.001	<0.001			-		<0.001
Standard	224	14	10 - 19		53		0		2	
Extended	205	36	21 - 56		12		100		67	
Missing	11									
Presacral lymphadenectomy										
				<0.001	<0.001			<0.001		-
No	280	14	10 - 19		53		19		0	
Yes	144	46	32 - 65		3		96		100	
Missing	16									
Geographic area										
				<0.001	<0.001			<0.001		<0.001
U.S.	388	20	13 - 39		30		48		37	
Non-U.S.	52	11	7 - 15		73		37		2	
Institution										
				<0.001	<0.001			<0.001		<0.001
#1	42	29	19 - 37		14		76		45	
#2	120	48	34 - 73		5		92		90	
Other	278	15	10 - 19		51		23		6	