Optimum Lymphadenectomy for Esophageal Cancer

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Objective: Using Worldwide Esophageal Cancer Collaboration data, we sought to (1) characterize the relationship between survival and extent of lymphadenectomy, and (2) from this, define optimum lymphadenectomy.

Summary Background Data: What constitutes optimum lymphadenectomy to maximize survival is controversial because of variable goals, analytic methodology, and generalizability of the underpinning data.

Methods: A total of 4627 patients who had esophagectomy alone for esophageal cancer were identified from the Worldwide Esophageal Cancer Collaboration database. Patient-specific risk-adjusted survival was estimated using random survival forests. Risk-adjusted 5-year survival was averaged for each number of lymph nodes resected and its relation to cancer characteristics explored. Optimum number of nodes that should be resected to maximize 5-year survival was determined by random forest multivariable regression.

Results: For pN0M0 moderately and poorly differentiated cancers, and all node-positive (pN+) cancers, 5-year survival improved with increasing extent of lymphadenectomy. In pN0M0 cancers, no optimum lymphadenectomy was defined for pTis; optimum lymphadenectomy was 10 to 12 nodes for pT1, 15 to 22 for pT2, and 31 to 42 for pT3/T4, depending on histopathologic cell type. In pN+M0 cancers and 1 to 6 nodes positive, optimum lymphadenectomy was 10 for pT1, 15 for pT2, and 29 to 50 for pT3/T4.

Conclusions: Greater extent of lymphadenectomy was associated with increased survival for all patients with esophageal cancer except at the extremes (TisN0M0 and ≥7 regional lymph nodes positive for cancer) and well-differentiated pN0M0 cancer. Maximum 5-year survival is modulated by T classification: resecting 10 nodes for pT1, 20 for pT2, and ≥30 for pT3/T4 is recommended.

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Increased number of regional lymph nodes containing metastases predicts decreased survival following esophagectomy for cancer,[1–6] and increased extent of lymphadenectomy is associated with improved survival.[1,7–12] Therefore, lymphadenectomy of some extent is required. However, what constitutes optimum lymphadenectomy to maximize survival is controversial.[1,8–11] Using Worldwide Esophageal Cancer Collaboration (WECC) data,[2] we sought to (1) characterize the relationship between survival and extent of lymphadenectomy, and from this, (2) define optimum lymphadenectomy.

METHODS

Worldwide Esophageal Cancer Collaboration

WECC is a consortium of institutions (Appendix 1, Supplemental Digital Content 1, available at: http://links.lww.com/SLA/A29) that has contributed deidentified patient data on esophagectomy for cancer. All datasets were approved for research by each site's institutional review board, and data use agreements were executed when required. The entire project was approved by the Case Cancer Institutional Review Board of Case Western Reserve University.

Patients

A total of 4627 patients underwent esophagectomy alone (no pre- or postoperative adjuvant therapy) for esophageal cancer and had follow-up for all-cause mortality.[2] Characteristics of these patients and their cancers are presented in Table 1, including number of regional lymph nodes resected (hereafter termed "nodes resected") and number of regional lymph nodes involved with cancer (hereafter termed "nodes positive," pN+). Although the analysis examined number of nodes resected and nodes positive in a continuous fashion, for illustration, number of nodes positive is separated into 4 groups: (1) no nodes positive, (2) 1 to 2 nodes positive, (3) 3 to 6 nodes positive, and (4) 7 or more nodes positive.

Data Analysis

Multivariable Risk-Adjusted Survival

Random survival forests (RSF) methodology[13,14] using the randomSurvivalForest R-package under its default settings[15] was employed to calculate a survival curve for each patient, adjusted for 45 variables (Appendix 2, Supplemental Digital Content 2, available at: http://links.lww.com/SLA/A30). These included TNM classifications, number of nodes resected, number of nodes positive (N), histopathologic cell type, histologic grade (G), location and length of cancer, residual cancer (R), patient demographics (age, race, gender), country, institution, and year of surgery.

For this, RSF analysis generated a forest of 1000 random "bootstrap survival trees," each grown using log-rank splitting. Missing nonanatomic and demographic data were imputed using a dynamic tree method.[14] On average, each bootstrap survival tree was constructed from 63% of the patients (bootstrapped data); the remaining 37% was referred to as out-of-bag (OOB) data. These OOB data and the corresponding bootstrap survival tree were used to generate an OOB "survival curve" for each patient in the OOB dataset. Growing 1000 trees yielded approximately 370 OOB sur-

TABLE 1. Patient and Esophageal Cancer Characteristics

Characteristic	n*	Mean ± SD or No. (% of n)
Demography		
Age (yr)	4625	62 ± 11
Men	4626	3562 (77)
Race	3587	
White		2339 (65)
Asian		1168 (33)
Other		80 (2.2)
Cancer location	4344	
Upper third		177 (4.1)
Middle third		1172 (27)
Lower third		2995 (69)
Cancer length	2229	3.3 ± 2.5
pT	4609	
is		335 (7.3)
1†		1040 (23)
2		755 (16)
3		2329 (51)
4		150 (3.3)
pN	4616	
0		2584 (56)
1		2032 (44)
Number of nodes positive	4507	
0	2584	(57)
1–2	900	(20)
3–6	599	(13)
7 or more	424	(9.4)
Number of nodes resected	3921	
0	42	(1.1)
1–5	986	(25)
6–10	740	(19)
11–15	558	(14)
16–20	444	(11)
21–25	337	(8.6)
26–30	219	(5.6)
31–35	152	(3.9)
36–40	112	(2.9)
≥41	331	(8.4)
pM	4564	
0		4208 (92)
1‡		356 (7.8)
Histopathologic cell type	4595§	
Adenocarcinoma		2775 (60)
Squamous		1834 (40)
Undifferentiated		7 (0.15)
Histologic grade	3816	
G1		1228 (32)
G2		1257 (33)
G3		1324 (35)
G4		7 (0.18)
Resection margins	4123	
R0		3572 (87)
R1		434 (11)
R2		117 (3.0)

*Number of cases with values available.
†pT1a in 262 and pT1b in 244 among 506 in whom this distinction was made.
‡pM1a in 104 and pM1b in 122 of 226 in whom this distinction was made.
§In 21, both cell types existed.

vival curves for each patient, which were averaged to yield a risk-adjusted OOB "ensemble survival curve." "Risk-adjusted OOB ensemble 5-year survival" was obtained by extracting the survival value at 5 years from these curves.[16]

Averaged Risk-Adjusted 5-Year Survival

Risk-adjusted OOB ensemble 5-year survival was averaged for all patients with a given number of nodes resected to yield "averaged risk-adjusted 5-year survival." Because histologic grade and histopathologic cell type were previously found to predict survival for pN0M0 (node negative, no distant metastases) cancers, but not for pN+M0 (node positive, no distant metastases) cancers,[16] separate analyses were performed for pN0M0 and pN+M0 cancers. For pN0M0 data, averaging was stratified by histologic grade and histopathologic cell type within T. For pN+M0 data, averaging was stratified by number of nodes positive within T.

Optimum Lymphadenectomy

Random forests multivariable regression (RF-R) was used to determine optimum number of nodes that should be resected (lymphadenectomy) to maximize 5-year survival.[17] For pN0M0 cancers, number of nodes resected, histologic grade, and location were independent variables, with risk-adjusted 5-year survival the response. For each combination of T and histopathologic cell type, regression was performed for those with number of nodes resected greater than or equal to a "fixed cutoff value" ranging from 0 to 50. Only combinations with more than 15 patients were analyzed. Each analysis generated 1000 random bootstrap regression trees. Computations were performed with the randomForest R-package under its default settings.[18]

For every cutoff value, RF regression yielded a "variable importance" (VIMP) value for each independent variable. VIMP measures predictiveness of a variable, adjusting for all other variables; it is the change in mean-square error of predicted 5-year survival after the variable is removed from the analysis. VIMP was standardized by dividing it by the variance of risk-adjusted 5-year survival and multiplying by 100, yielding values from −100% to 100%. A standardized VIMP >0 signifies a predictive variable; however, a threshold of 5% was used for this study to define "predictiveness." This threshold accounts for Monte Carlo and sampling variability. For each stratification, optimum number of nodes resected was determined by the value at which standardized VIMP first dropped below 5%.

For pN+M0 cancers, a similar RF-based strategy was used. Data were stratified by number of nodes positive within T: 1 or 2, 3 to 6, and 7 or more. Number of nodes resected and number of nodes positive were used as independent variables (the latter was included to allow for more precise prediction, even though data were stratified into node-positive groupings). Standardized VIMP was calculated for number of resected nodes, stratified by number of nodes positive within T classification.

RESULTS

Survival and Extent of Lymphadenectomy

pN0M0 Cancers

For patients with pTis cancers, regardless of histopathologic cell type, survival was excellent and not associated with extent of lymphadenectomy (Fig. 1A). For patients with T1N0M0 cancers, survival was unrelated to extent of lymphadenectomy for G1 cancers (Fig. 1A), but increased with more extensive lymphadenectomy for G2/G3 cancers (Fig. 1B). For patients with pT2N0M0 and pT3/T4N0M0 cancers, there were few G1 cancers with extensive lymphadenectomy (Fig. 1A), but the limited data suggest survival was unrelated to extent of lymphade-

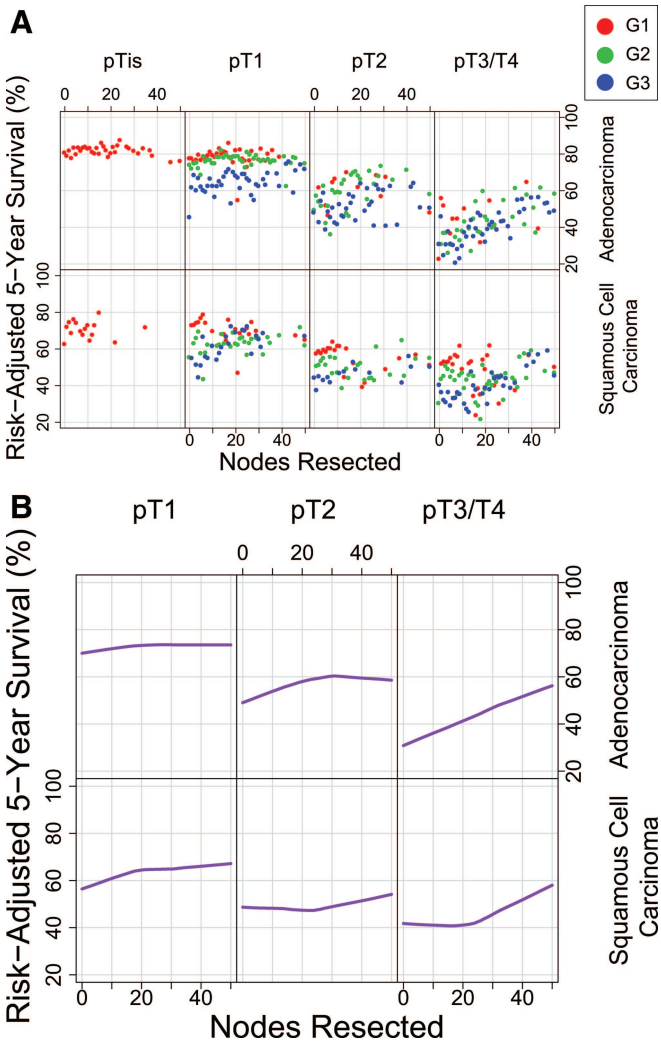

FIGURE 1. Coplot of averaged risk-adjusted 5-year survival after esophagectomy for pN0M0 cancers according to number of nodes resected, pT classification, and histopathologic cell type. A, Raw data. Each dot represents an average for a node resected. Colors represent histologic grade (see key). B, G2/G3 cancers with survival displayed as smooth loess curves according to number of nodes resected.

nectomy; however, for G2/G3 cancers, 5-year survival increased with extent of lymphadenectomy (Fig. 1B).

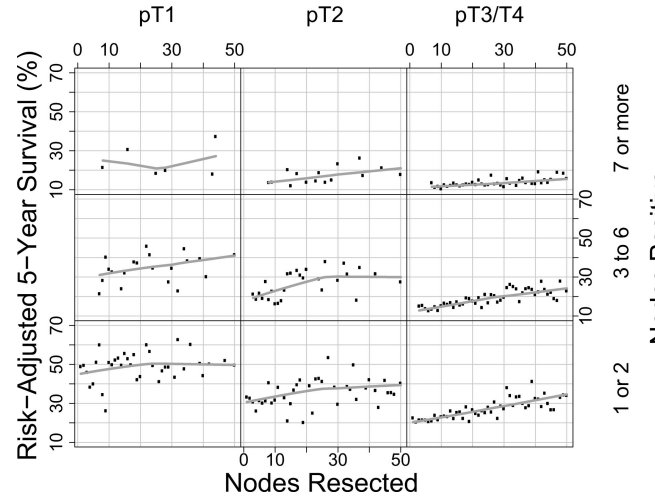

FIGURE 2. Coplot of averaged risk-adjusted 5-year survival after esophagectomy for pN+M0 cancers according to number of nodes resected, T classification, and number of nodes positive. Solid lines are loess smoothed curves.

pN+M0 Cancers

For patients with pN+M0 cancers and 1 to 6 nodes positive, survival increased with extent of lymphadenectomy for all T classifications (Fig. 2). For patients with 7 or more nodes positive, survival increased, albeit minimally, with extent of lymphadenectomy for T2 and T3/T4 cancers. Paucity of pT1 cancers with 7 or more nodes positive precluded assessing the survival value of lymphadenectomy.

pN0/pN+ Distinction

For pT3/T4 N0M0 cancers, patients with minimal lymphadenectomy (Fig. 1B) have survival equivalent to patients with pT3/T4 N+M0 cancers with moderate to extensive lymphadenectomy and 1 to 6 nodes positive (Fig. 2). For pN+M0 cancers, for the same T classification, extensive lymphadenectomy yielded 5-year survival similar to minimal lymphadenectomy for one lower node-positive grouping (Table 2).

Optimum Lymphadenectomy

For pTis, no optimum extent of lymphadenectomy could be identified (Fig. 3A). For pT1 cancers, optimum lymphadenectomy was 10 for N0M0 adenocarcinomas and 12 for N0M0 squamous cell carcinomas (Fig. 3A), and 10 for 1 to 6 nodes positive (insufficient data were available for 7 or more nodes positive) (Fig. 3B). For pT2 cancers, optimum lymphadenectomy was 15 for N0M0 adenocarcinomas and 22 for N0M0 squamous cell carcinomas (Fig. 3A), and

TABLE 2. pTN Classifications With Similar Survival, Illustrating Survival Difference Between Minimal and Extensive Lymphadenectomy

Extensive Lymphadenectomy				Minimal Lymphadenectomy			
pT	Nodes Positive	Nodes Resected	5-yr Risk-Adjusted Survival (%)	5-yr Risk-Adjusted Survival (%)	Nodes Resected	Nodes Positive	pT
T1	3–6	≥35	40	42	<5	1–2	T1
T1	≥7	≥35	28	31	≤10	3–6	T1
T2	3–6	≥35	28	31	≤5	1–2	T2
T2	≥7	≥35	21	20	≤10	3–6	T2
T3/T4	3–6	≥35	23	21	≤5	1–2	T3/T4
T3/T4	≥7	≥35	15	14	≤10	3–6	T3/T4

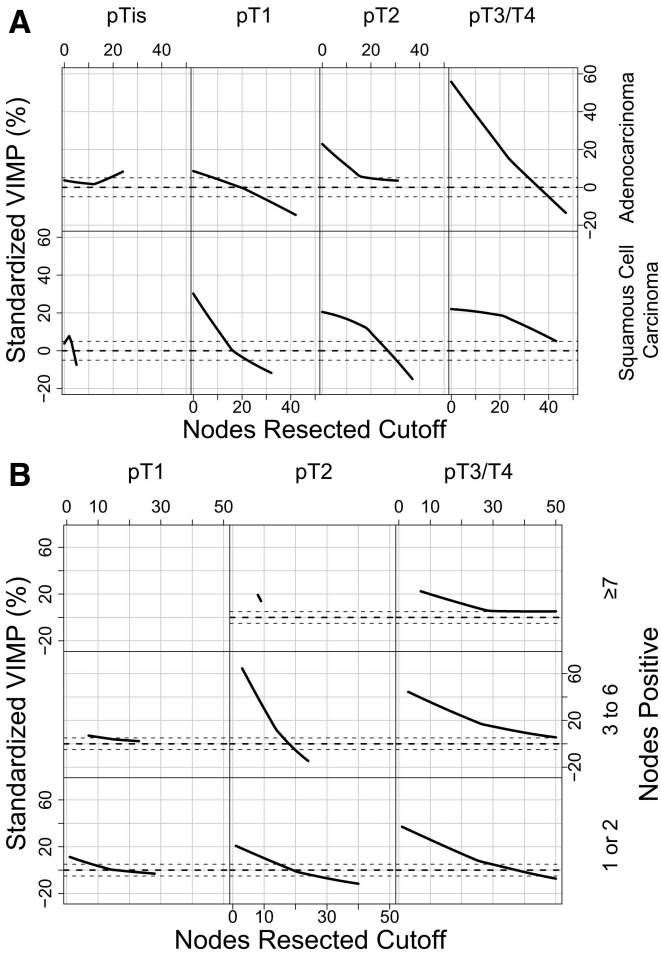

FIGURE 3. Standardized variable importance (VIMP) for a series of cutoff values for number of nodes resected according to T classification. A, pN0M0 cancers, stratified by histopathologic cell type. B, pN+M0 cancers, stratified by number of nodes positive.

15 for 1 to 6 nodes positive (insufficient data were available for 7 or more nodes positive) (Fig. 3B). For pT3/T4 cancers, optimum lymphadenectomy was 31 for N0M0 adenocarcinomas and 42 for N0M0 squamous cell carcinomas (Fig. 3A), and 29 for 1 to 2 nodes positive, 50 for 3 to 6 nodes positive, and 28 for 7 or more nodes positive (Fig. 3B).

DISCUSSION

Principal Findings and Uniqueness of Analysis

Based on worldwide data, extent of lymphadenectomy was either unassociated with or minimally increased survival for patients with extremes of esophageal cancer (TisN0M0 and 7 or more nodes positive) and those with well-differentiated pN0 cancer. Five-year survival improved with increasing extent of lymphadenectomy for all other pN0 and pN+ cancers. RF analysis identified optimum lymphadenectomy for each pT and confirmed the interplay of depth of tumor invasion (T) and N+.[19,20] Whether the effect of lymphadenectomy is stage purification or therapy cannot be resolved completely from this study. For example, survival after minimal lymphadenectomy for pT3/T4N0 cancers is equivalent to that of pT3/T4N+ cancers with 1 to 6 positive nodes after moderate to extensive lymphadenectomy; we believe this represents stage purification. However, for pN+ cancers, improved survival with more extensive lymphadenectomy may relate to more accurate determination of number of positive nodes (stage purification), or therapeutic effect of removing micrometastases.

A unique aspect of this study is that optimal lymphadenectomy was obtained using a new machine-learning technique. The technique is related to traditional recursive partitioning analysis, which has been used extensively in analysis of cancer survival data.[1,21] However, random forest (RF) analyses introduce randomization by bootstrapping the data to result in multiple (hundreds to thousands) of trees. What is generally found is that each bootstrapped tree is a different result. Thus, any given tree (or recursive partitioning analysis) is unstable.[22] But when a forest of such trees is summarized (aggregated), a stable result emerges.[14] Like all varieties of RF analysis, RSF analysis makes no a priori assumptions about survival as do model-based analyses, which may assume proportional hazards, a particular formulation of a risk factor model, and a specific form for interaction terms. Most importantly, because trees in the forest use recursive partitioning, RSF is able to identify complex interactions between variables and nonlinear relationships,[14,17] something that is difficult to do using parametric and semiparametric methods.

VIMP was used to define optimal lymphadenectomy. Rather than examining goodness of fit or *P* values to test for a statistically significant effect, the present analysis focused on predictiveness for future patients. Because VIMP uses RF regression, it is nonparametric and therefore has the same advantages as RSF.

Stratification of the VIMP analysis by T, histopathologic cell type, and N+, and use of histologic grade, tumor location, and number of nodes resected and positive as independent variables, refined the determination of optimal lymphadenectomy. Use of nonanatomic tumor characteristics and demographic variables in addition to TNM was based on previously identifying these as crucial correlates of survival.[16]

Limitations

Extent of lymphadenectomy did not occur according to a uniform protocol and so was highly variable. Similarly, there was no uniform protocol for pathologic review of the resection specimen. We exploited this heterogeneity to investigate optimal lymphadenectomy. Despite worldwide data, there was a paucity of cases at the extremes, such as well-differentiated pT3/T4N0 and pT1/T2 with 7 or more nodes positive; this relates as much to biology as to the study. The measure of optimal lymphadenectomy was all-cause mortality, which includes a few noncancer deaths, but nevertheless, it is a reliable end point and the basis for most cancer staging.[23,24] We did not have morbidity information according to extent of lymphadenectomy, although hospital mortality was low.[2] The main problem is that each institution has a different method of counting the number of lymph nodes resected. Some pathology laboratories may not be as fastidious as others and therefore provide an artificially low count.

Quest to Define Optimum Lymphadenectomy

For many investigators, the quest to define optimum lymphadenectomy has focused on discovering a single number for nodes resected. Evidence from our study indicates that an increasing extent of lymphadenectomy is associated with progressively increased survival that plateaus—a nonlinear effect. There is no single number.

Few have investigated the possibility that adequacy of lymphadenectomy-only depends on cancer characteristics—what might be called an "interaction" effect.[1,8] Where it has, as in the present study, an important difference in optimum lymphadenectomy has been found that varies with cancer characteristics.

Mechanics of analysis also has influenced defining optimum lymphadenectomy. Some have formally considered a nonlinear relationship, such as we have found,[1,8] others have assumed a linear effect,[10,11] and still others have arbitrarily grouped data as a form of acknowledging nonlinear effects.[9,12] In addition, the statistical criterion for defining an optimum lymphadenectomy has differed. Most have focused on prognosis, either maximizing survival or minimizing hazard; however, others have focused on goodness of fit to minimize classification error.[10,11]

Generalizability of results plays a role. Many studies are from a single institution with a relatively small number of patients.[1,8,12] Others use epidemiologic databases not designed specifically for studying lymphadenectomy.[9,10] We and others[11] have used worldwide data from multiple institutions because this is an uncommon cancer, and its characteristics differ geographically.

Finally, some have avoided number of nodes resected and simply compared fields of dissection (transhiatal, 2- and 3-field lymphadenectomy).[7] Extent of lymphadenectomy in such analyses is surgeon dependent and so is coarse and highly variable.

All of these analyses have led to different recommendations for extent of lymphadenectomy.

Rizk et al[1] used recursive partitioning analysis to study 336 esophagectomies from a single institution. They identified 18 nodes resected as the minimum necessary for accurate staging and for eliminating an effect of lymphadenectomy on survival.

Altorki et al[8] used proportional hazards multivariable analysis of 264 esophagectomies from a single institution. Patients were stratified into 4 groups by number of nodes resected. Effect of lymphadenectomy on survival was lost after 25 nodes resected for early-stage disease and after 16 nodes in stage III and IV cancers.

Greenstein et al[9] used both univariable log-rank tests of stratified Kaplan-Meier survival curves and multivariable proportional hazards regression with SEER data (1998 to 2003) from 972 esophagectomies. Patients were stratified by number of nodes resected. Survival progressively increased with increased extent of lymphadenectomy in pN0 cancer. They recommended resecting at least 18 lymph nodes.

Schwarz and Smith[10] used multivariable proportional hazards analysis of SEER data (1970 to 2003) of 5620 esophagectomies. Thirty or more nodes resected was associated with best survival.

Peyre et al[11] used logistic and Cox regression analysis of an international database of 2303 esophagectomies. Goodness of fit to survival was maximized with 23 to 29 nodes resected.

Recommendations

If there is uncertainty as to T and histopathologic grade, it is recommended that 30 or more nodes be resected to maximize 5-year survival. Preoperative assessment requires biopsy of the cancer to determine histopathologic cell type and histologic grade, and endoscopic esophageal ultrasound to determine cT, which is a reasonably accurate reflection of pT.[25,26] It is recommended that to maximize 5-year survival, a minimum of 10 nodes be resected for T1 cancer, 20 nodes for T2 cancer, and 30 or more nodes for T3/T4 cancers. True extent of lymphadenectomy is best assured when the surgeon separates the nodal material from the specimen, sending separate "packets of nodal material" to the pathology laboratory;[27] however, care must be exercised in recovering nodes surrounding the primary cancer so as not to obscure the radial resection margin.

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