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Predictors of Residual Disease after Unplanned Excision of Soft Tissue Sarcomas

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Abstract

Background—Unplanned excision of soft tissue sarcomas (STS) is an important quality of care issue given the morbidity related to tumor bed excision. Since not all patients harbor residual disease at the time of re-excision, we sought to determine predictors of residual STS following unplanned excision.

Methods—We identified 76 patients from a prospective database (1/1/2008 – 9/30/2014) who received a diagnosis of primary STS following unplanned excision on the trunk or extremities. We used univariable and multivariable analyses to evaluate predictors of residual STS as the primary endpoint. We calculated the sensitivity/specificity and accuracy of interval magnetic resonance imaging (MRI) to predict residual sarcoma at re-excision.

Results—Mean age was 52 years, and 63.2% were male. 50% had fragmented unplanned excision. Among patients undergoing re-excision, residual STS was identified in 70%. On univariable analysis, MRI showing gross disease and fragmented excision were significant predictors of residual STS (OR 10.59, 95% CI 2.14–52.49, P=0.004 and OR 3.61, 95% CI 1.09–11.94, P=0.035, respectively). On multivariable analysis, tumor size predicted distant recurrence

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and overall survival. When we combined equivocal and positive MRI, the sensitivity and specificity of MRI for predicting residual STS were 86.7% (95% CI 73.2–95.0%) and 57.9% (95% CI 33.5–79.8%), with an overall accuracy of 78.1% (95% CI 66.0–87.5%).

Conclusions—70% of patients undergoing repeat excision after unplanned excision of STS harbor residual sarcoma. Although interval MRI and fragmented excision appear to be the most significant predictors of residual STS, the accuracy of MRI remains modest, especially given the incidence of equivocal MRI.

Keywords

Soft tissue sarcoma; unplanned excision; MRI; residual disease

Introduction

Because soft tissue sarcomas (STS) are rare, it is not uncommon for physicians to excise a soft tissue mass without further work up, assuming it is a lipoma, lymph node, or hematoma. If the soft tissue mass proves to be an unsuspected STS, this approach is referred to as an "unplanned excision."[1–4]

From a quality of care perspective, unplanned excisions are problematic, as STS extends beyond its pseudocapsule, leading to an increased risk of residual disease and local recurrence. Furthermore, long-term control of disease may be compromised following an unplanned excision.[2, 5–7]

When an unplanned excision occurs, there is no attention to the pursuit of tumor-free margins, and the oncologic nature of the unplanned excision is considered marginal at best. Repeat excision allows for a properly planned total resection. As a result, the standard recommendation following unplanned excision of STS is re-excision of the tumor bed to optimize oncologic outcome.[1, 5, 8]

Despite the oncologic benefits of repeat resection after unplanned excision, this approach is clearly associated with greater morbidity.[5] Furthermore, although studies have demonstrated improved local control and survival with wide margin re-excision after unplanned excision,[9] other studies have shown no oncologic benefit to re-excision.[2] Studies attempting to explain this discrepancy have suggested that microscopic residual disease remaining after re-excision may be a marker of clinical aggressiveness.[3, 10]

Given the association of residual sarcoma after unplanned excision with worse survival as well as the significant potential surgical and functional morbidity, the ability to predict residual disease prior to repeat excision could permit a more tailored approach to repeat resection and combined modality therapy. This information may translate to improved patient risk stratification and limit additional surgical morbidity in patients unlikely to harbor residual disease.[11, 12] Since not all patients harbor residual sarcoma following unplanned excision, we sought to analyze predictors of residual sarcoma following unplanned excision of STS, hypothesizing that these data may serve as baseline information

for future prospective evaluation of a selective, algorithmic approach to tumor bed management following unplanned excision.

Materials and Methods

From January 2008 to September 2014, 76 patients underwent unplanned excision of STS located on the trunk or extremity and presented to our sarcoma referral center for further evaluation and management recommendations. These patients were identified from a prospectively maintained cancer center database, and all patients were reviewed in a multidisciplinary Sarcoma Tumor Board. Patients with fibromatosis (N=17) and gynecological sarcomas (N=22) were excluded from this analysis. We also excluded patients who underwent an incisional biopsy.

This study was approved by the Institutional Review Board. Since it was considered no more than minimal risk, a waiver of consent was obtained. We then abstracted clinical, pathologic, and treatment data, including age, gender, tumor location, stage at presentation, histologic type, maximal tumor diameter, histologic grade, tumor depth, margin status, presence of fragmented excision, presence of repeat excision, time interval between unplanned excision and re-excision, results of interval magnetic resonance imaging (MRI), presence of residual STS following resection, local and distant recurrence. Pathology reports were used to determine fragmented excision, as the description of the gross specimen was very specific for one piece or fragments. Local-recurrence free (LRFS), distant-recurrence free (DRFS), disease-specific (DSS), and overall survival (OS) were calculated as described previously.[13, 14]

Tumor size was analyzed as a continuous variable using maximal tumor dimension from initial pathological evaluation. Tumor sites included extremity (upper at or distal to the shoulder/axilla, and lower at or distal to the buttock/groin) and trunk. Retroperitoneal and visceral tumors were excluded. Histologic grade was classified using a three-tiered system (grade I through III) according to established criteria.[15]

Histologic diagnosis was assigned by the published criteria of the World Health Organization Classification of Tumors of Soft Tissue and Bone.[15] For purposes of statistical analysis, we limited our analysis to six histology categories, including “other” which represented a composite of synovial sarcoma, extraskeletal myxoid chondrosarcoma, solitary fibrous tumor, angiosarcoma, fibromyxoid sarcoma, clear cell sarcoma, epithelioid sarcoma, primitive neuroectodermal tumor, and sarcoma, NOS.

Tumor bed re-excision included an en-bloc resection of the entire tumor bed with a two centimeter margin while avoiding entry into the tumor bed/seroma cavity. Final margin status was determined either clinically (R2 for gross residual tumor left behind) or as part of the histopathologic assessment (R1 for microscopically positive margins, and R0 for microscopically negative margins). Given the low rate of R2 disease (N=1), data were analyzed in two groups: margin negative (R0) or margin positive (R1/R2).

The date of recurrent disease was defined either by biopsy or by the radiologic detection of suspicious lesions when no biopsy was performed. Follow-up was counted from the date of

diagnosis until the date of death or date of last follow-up. Freedom from local recurrence was counted from the date of resection. Patients who were free from recurrence or death were censored according to the date of their last follow-up.

Interval MRIs were considered positive if reported as consistent with gross residual disease (focal or discrete enhancing mass). MRIs interpreted as no evidence of residual disease were considered negative. There was a subset of MRIs showing “non-specific tumor bed enhancement,” and these were classified as equivocal. All MRIs were reviewed by the multi-disciplinary tumor board.

Summary statistics were reported as mean ± standard deviation (SD) with median (range) where appropriate. Logistic regression was used to evaluate predictors of residual sarcoma. Sensitivity, specificity, and accuracy of MRI to predict residual sarcoma compared to the gold standard pathological assessment of the tumor bed excision specimen were calculated according to standard definitions.[16] Cox PH regression was used to assess predictors of each of the oncologic outcomes.[17] Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Significance was set at $P < 0.05$.

Results

Patient and Tumor Characteristics

The clinico-pathologic characteristics of the patient cohort are depicted in Table 1. The median age was 52.0, and 36.8% were female. Extremity was the most common primary site. The median maximal tumor diameter was 7.0 cm with a significant range of tumor size from 0.5 – 32.0 cm. 52.6% of tumors were high grade, and 79.0% were deep to the fascia. Thirteen different sarcoma histologies were represented, but the majority of tumors were comprised of high grade undifferentiated pleomorphic sarcoma, leiomyosarcomas, and liposarcomas (59%).

Of the 76 patients in the study, 38 patients (50%) had fragmented excision at the time of initial unplanned excision. Repeat excision was performed in 64 patients (84%). Twelve patients did not undergo re-excision for miscellaneous reasons including prohibitive morbidity (N=4), prolonged time delay from unplanned excision to referral for repeat excision (N=3), non-compliance with treatment (N=3), and change in goals of care (N=2). R0 resection was achieved in 78.4% of patients, while 20.3% had an R1 resection, and 1 patient (1.3%) had an R2 resection.

There were four patients in total who received interval radiation therapy (three with undifferentiated pleomorphic sarcoma and one with pleomorphic liposarcoma) prior to planned, definitive resection. In addition, there were two patients who received interval chemotherapy prior to definitive surgical resection, including one patient with primitive neuroectodermal tumor (Ewing’s sarcoma) and one patient with a high grade sarcoma, not otherwise specified. We did not have any patients in this cohort who received both radiation therapy and chemotherapy prior to repeat excision. Overall, only a small minority of our cohort (9%, 7/76) received adjuvant/neo-adjuvant chemotherapy, while radiation therapy was administered to 30 patients (40%), but 58% of patients with high grade tumors (23/40).

MRI as a Predictor of Residual Disease

Prior to re-excision, interval MRI was read as positive for residual tumor in 28 patients (43.8%), negative in 17 (26.6%), and equivocal in 19 (29.7%). Following repeat resection, final pathology revealed residual tumor in 45 patients, or 70%. On univariable logistic regression analysis (Table 2), a positive interval MRI and fragmented unplanned excision were the only statistically significant variables identified as a predictor of residual sarcoma (OR 10.59, 95% CI 2.14–52.49, P=0.004 and OR 3.61, 95% CI 1.09–11.94, P= 0.035).

With nearly one-third of patients found to have an equivocal MRI, we elected to analyze the data further by classifying an equivocal MRI as either positive or negative in order to assess the impact of equivocal MRI on sensitivity and specificity of the test. As depicted in Table 3A, of the 36 patients with a negative or equivocal MRI, 19 (52.8%) had residual sarcoma identified at re-resection. When equivocal MRIs were categorized as negative, the sensitivity and specificity of MRI were 57.8% and 89.5%, respectively. This analysis yielded an accuracy of MRI of 67.2%.

Conversely, as shown in Table 3B, when equivocal interval MRIs were categorized as positive for residual disease, there were 39 of 47 patients (83%) with a positive MRI who had residual STS at re-excision. Excluding the equivocal MRIs, 26 of the 28 patients with a positive MRI had residual disease (93%). In contrast, six patients of 17 patients (35%) with negative MRIs were found to harbor residual disease at re-resection. When analyzing equivocal interval MRIs in this fashion, the sensitivity and specificity of interval MRI were 87% and 58%, respectively, and the accuracy increased to 78%. Overall, 13 of 19 patients (68%) with an equivocal interval MRI were found to harbor residual STS at re-excision, underscoring the limitations of this imaging modality to predict residual sarcoma.

Oncologic Outcome in Multivariable Cox Regression Analysis

On multivariable Cox regression analysis, we were unable to identify any statistically significant predictors of time to residual disease or local recurrence. As depicted in Tables 4 and 5, tumor size was the sole statistically significant predictor of both time to distant recurrence and OS (HR 1.16, CI 1.02–1.32, P=0.02 and HR 1.20, CI 1.02–1.41, P=0.033). Of note, we chose to omit treatment-related variables (i.e., receipt of chemotherapy or radiotherapy) from the multivariate model since their association with the outcome of survival and distant recurrence could not be assumed to be independent.

Discussion

The term “unplanned excision” is used to describe a non-oncologic resection of a STS and was first described by Giuliano et al. in 1985.[1] These procedures are characterized by a failure to pursue tumor-free margins and are typically performed without preoperative imaging or a tissue diagnosis. As a result, the occurrence of unplanned excision is a significant quality of care issue, and the standard recommendation after unplanned excision of STS is tumor-bed excision in an attempt to ensure complete resection of the tumor and to maximize oncologic outcome. However, there are clearly acute and chronic morbidities

related to tumor bed excision, and these morbidities can be significant, especially in the setting of combined modality therapy for STS.

In addition, it is important to note that the ultimate oncologic impact of unplanned excision of STS remains controversial. In most studies, tumor bed excision following unplanned excision has been associated with superior oncologic outcome, including improved LRFS and OS, compared to unplanned excision alone.[2, 3, 8–10] However, when comparing tumor bed excision following unplanned excision to planned complete excision as the initial procedure, some studies have observed inferior overall oncologic outcomes even when repeat resection is performed, suggesting that there is an adverse oncologic effect of unplanned excision.[6, 7] Conversely, other studies have shown equivalent oncologic outcomes between matched cohorts of tumor bed excision patients after unplanned excision compared to planned complete excision as the initial procedure, suggesting that oncologic outcomes are dictated by final surgical results.

Moreover, an important study by Lewis et al. even observed improved oncologic outcomes among STS patients who underwent repeat resection after an initial unplanned excision compared to patients who underwent a single resection at a tertiary cancer hospital, suggesting that unplanned excision was associated with a favorable oncologic outcome.[18] Ultimately, a true assessment of the impact of unplanned excision on oncologic outcome in STS is limited since all studies of this nature are retrospective and therefore subject to the effects of selection bias and confounding. Clearly, however, patients who are subjected to repeat resection following unplanned excision are exposed to greater acute and chronic surgical morbidity from two operations rather than one. The landmark study on this topic was reported by Mankin et al. who observed that a more invasive or complex operation was necessary in 19% of 597 patients following an inappropriately performed incisional or excisional biopsy, leading, in some cases, even to amputation.

Our study sought to determine predictors of residual STS following re-excision with the future goal of predicting which patients may be spared from excess morbidity of re-excision while still accurately stratifying risk for local and distal recurrence. Although fragmented excision and suspicious MRI were identified on univariate analysis as significant predictors of residual STS, no clear risk factor was identified on multivariate analysis. Moreover, the predictive value of MRI was modest, and the results of interval MRI following unplanned excision must be considered in the complete clinical context, especially given the significant occurrence (30%) of equivocal MRI.

A review of the literature reveals a wide range in the incidence of residual STS when re-excision is performed following unplanned excision. Most studies report residual sarcoma in approximately 50% of patients, but there is a wide range from as low as 24% to as high as 91%.[19–21] Our study, from a prospectively maintained database, identified residual STS in 70% of patients, reinforcing the impression that residual STS is an important problem following unplanned excision.

The utility of MRI as a predictor of residual disease in STS following unplanned excision has received less attention. A 2004 study showed that despite a low negative predictive

value, MRI remains useful in identifying the size of residual tumor.[21] Meanwhile, a 2010 study showed residual tumor was not readily distinguished from postoperative change in STS of the hand.[22] Post-surgical changes had the greatest impact on the accuracy of MRI, as surrounding edema, hematoma and seroma create a distorted picture from which it is difficult to exclude macroscopic disease.[21, 22] While MRI is undoubtedly useful for surgical planning, interpretation of the results with respect to residual tumor following unplanned excision must be carefully considered.

Unlike other studies, we did not observe tumor location to be a significant predictor of residual disease after unplanned excision. Goodlad et al. analyzed 95 patients who underwent re-excision following unplanned excision.[20] These authors observed that tumors located near the ankle were more likely to harbor residual disease as opposed to the thigh. In our analysis, we limited our analysis to extremity and trunk and did not investigate the impact of anatomic sub-site because of our sample size. Differences in study design such as these may bias our results and are therefore an important area for future research.

While this is a single-center analysis of 76 patients, it is important to acknowledge potential limitations of our study. Notably, 12 patients in our series did not undergo tumor bed excision (for various reasons as noted above). This suggests that an element of selection bias is already evident in the approach to STS patients after unplanned excision, and inclusion of these patients in the re-excision group would potentially impact the incidence of residual disease and the accuracy of MRI in our analysis.

Another limitation to this study is the low numbers for some histologic subtypes, which precluded us from evaluating histology as a precise predictor of residual sarcoma in our univariate and multivariate models. Given the limited numbers of certain subtypes as well as the number of histologies represented, our statistical power to evaluate histology as a predictor of STS is low, and we hypothesize that histologic subtype likely is an important predictor variable of residual disease which we were not able to demonstrate in our analysis. Given the 50 – 100 different subtypes of STS, it is paramount to consider the heterogeneity of STS behavior and the relative local aggressiveness of certain subtypes versus others, particularly in the context of unplanned excision and assessing the indications for a re-excision.

It is also important to acknowledge that interval radiation therapy and chemotherapy were received by a small subset of our patients prior to definitive surgical resection. While this may introduce a bias in terms of the probability of identifying residual STS at re-excision, the number of patients was too small to analyze these patients. In order to maximize our sample size, we chose to include these patients rather than exclude them, but we do acknowledge this as a confounding factor in our analysis.

Finally, we recognize that time to recurrence and overall survival may be influenced by the receipt of combined modality therapies such as chemotherapy and radiotherapy. However, current guidelines more strongly favor routine adjuvant therapies for higher risk patients with high grade and/or larger tumors, while adjuvant therapies in lower risk patients (low grade and/or smaller tumors) are frequently omitted from the treatment plan or applied

selectively. As a result, we chose to omit treatment-related variables from the multivariate model since their association with the outcome of survival and distant recurrence could not be assumed to be independent, acknowledging that these are important variables which impact oncologic outcome.

Ultimately, we observed that the sensitivity, specificity, and accuracy of interval MRI are subject to interpretation, especially when considering equivocal MRIs. It can be difficult to delineate neoplasia from post-surgical changes in the tumor bed. The ability to do so will vary based on image quality, patient anatomy, and the experience of radiologists and surgeons reviewing the images. In our analysis, the accuracy of MRI was improved if equivocal/non-specific MRIs were assumed to be positive. Therefore, the utility of MRI in guiding the clinical decision-making process must be taken in a greater context. In our judgment, a positive MRI in the setting of fragmented excision clearly indicates a need for re-excision, but an equivocal or even negative MRI does not rule out the justification for a tumor bed excision because of the possibility of harboring microscopic residual STS which may be occult or non-specific on MRI.

Consequently, further studies are needed to determine the optimal approach to tumor bed management following unplanned excision of STS. Given the morbidity of re-excision, a selective approach to repeat excision could translate into improved functional outcomes for patients. However, given the high incidence of residual disease and the modest utility of MRI, re-excision remains the default recommendation for now.

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Table 1

Clinical-pathological Characteristics (N=76)

	N (%)
Age at Diagnosis mean ± SD (median; range)	52.0±18.6 (55; 6 – 86)
Gender	
Female	28 (37%)
Male	48 (63%)
Tumor Size mean ± SD (median; range)	7.0±6.2 (5; 0.5 – 32)
Tumor Location	
Extremity	56 (74%)
Trunk	20 (26%)
Grade *	
High	40 (53%)
Intermediate	11 (14%)
Low	23 (30%)
Depth	
Deep	60 (79%)
Superficial	16 (21%)
Histology	
HGUPS	20 (26%)
Liposarcoma¶	16 (21%)
Leiomyosarcoma	9 (12%)
MPNST	8 (11%)
DFSP	4 (5%)
Other#	19 (25%)
Fragmented Excision	
Yes	38 (50%)
No	38 (50%)
Final Margins	
R0	58 (78%)
R1	15 (20%)
R2	1 (1%)
Residual Sarcoma	
Yes	45 (70%)
No	19 (30%)

[*] For 2 patients, grade was unknown/missing.

[¶] Includes 9 well-differentiated liposarcoma, 4 myxoid liposarcoma, and 2 dedifferentiated liposarcoma

[#] Includes 7 synovial sarcoma, 2 extraskeletal myxoid chondrosarcoma, 2 solitary fibrous tumor, 2 angiosarcoma, 2 fibromyxoid sarcoma, 1 clear cell sarcoma, 1 epithelioid sarcoma, 1 primitive neuroectodermal tumor, and 1 sarcoma, NOS.

Table 2

Univariable Logistic Regression Analysis of Predictors of Residual Sarcoma

Variable	Odds Ratio for Residual Sarcoma Following Repeat Excision (95% Confidence Interval)	P value
Sex		0.77
Female	referent	
Male	1.19 (0.38 – 3.70)	
Location		0.53
Extremity	referent	
Trunk	1.52 (0.42 – 5.50)	
Size	1.19 (0.99 – 1.45)	0.07
Grade		0.06
Low	referent	
Intermediate	0.18 (0.03 – 1.00)	
High	1.22 (0.33 – 4.60)	
Depth		0.71
Superficial	referent	
Deep	1.27 (0.36 – 4.42)	
Histology		0.23
HGUPS	referent	
Liposarcoma	1.11 (0.20 – 6.18)	
Leiomyosarcoma	0.20 (0.03 – 1.24)	
MPNST	0.33 (0.04 – 3.21)	
Other *	1.33 (0.28 – 6.44)	
Interval MRI #		0.004
Negative	referent	
Positive	10.59 (2.14 – 52.49)	
Fragmented Unplanned Excision		0.035
No	referent	
Yes	3.61 (1.09 – 11.94)	

* There were numerical problems when analyzing the histology using 6 categories, so DFSP was included with the Other category.

MRI scans showing “non-specific tumor bed enhancement” were classified as negative.

Table 3

A: Contingency Table of Interval MRI and Residual Sarcoma Classifying Equivocal MRI as Negative			
Interval MRI	**Residual Sarcoma**		
	Yes	**No**	**Total**
Positive	26	2	28
Negative	19	17	36
Total	45	19	64

B: Contingency Table of Interval MRI and Residual Sarcoma Classifying Equivocal MRI as Positive			
Interval MRI	**Residual Sarcoma**		
	Yes	**No**	**Total**
Positive	39	8	47
Negative	6	11	17
Total	45	19	64

Sensitivity: 57.8% (95% confidence interval: 42.1 – 72.3%)
Specificity: 89.4% (95% confidence interval: 66.9 – 98.7%)
Accuracy: 67.2% (95% confidence interval: 54.3 – 78.4%)
Sensitivity: 86.7% (95% confidence interval: 73.2 – 95.0%)
Specificity: 57.9% (95% confidence interval: 33.5 – 79.8%)
Accuracy: 78.1% (95% confidence interval: 66.0 – 87.5%)

Table 4

Multivariable Cox Proportional Hazards Regression Analysis of Predictors of Time to Distant Recurrence

Variable	Hazard Ratio for Residual Sarcoma Following Repeat Excision (95% Confidence Interval)	P value
Sex		0.66
Female	referent	
Male	1.34 (0.37 – 4.91)	
Location		0.06
Extremity	referent	
Trunk	0.16 (0.03 – 1.06)	
Size	1.16 (1.02 – 1.32)	0.02
Grade		0.08
Low	referent	
Intermediate	-- *	
High	6.81 (1.27 – 36.61)	
Depth		0.88
Superficial	referent	
Deep	1.19 (0.13 – 10.99)	
Histology		0.22
HGUPS	referent	
Liposarcoma	0.39 (0.03 – 5.03)	
Leiomyosarcoma	-- *	
MPNST	4.06 (0.55 – 29.87)	
Other *	3.50 (0.81 – 15.22)	
Fragmented Unplanned Excision		0.69
No	referent	
Yes	1.33 (0.32 – 5.48)	
Final Margin #		0.96
R0	referent	
R1/R2	0.90 (0.01 – 81.90)	
Repeat Excision		0.71
Yes	referent	
No	2.31 (0.03 – 202.68)	

* Hazard ratios for these sub-groups were not defined.

There were numerical problems when analyzing the histology using 6 categories, so DFSP was included with the Other category.

¶ Given the low rate of R2 disease (N=1), data were analyzed in two groups: margin negative (R0) and margin positive (R1/R2).

Table 5

Multivariable Cox Proportional Hazards Regression Analysis of Predictors of Overall Survival

Variable	Hazard Ratio for Residual Sarcoma Following Repeat Excision (95% Confidence Interval)	P value
Sex		0.84
Female	referent	
Male	1.20 (0.21 – 6.88)	
Location		0.40
Extremity	referent	
Trunk	0.40 (0.05 – 3.32)	
Size	1.20 (1.02 – 1.41)	0.033
Grade		0.15
Low	referent	
Intermediate	-- *	
High	34.91 (0.97 – 1,256.92)	
Depth		0.99
Superficial	referent	
Deep	-- *	
Histology		0.72
HGUPS	referent	
Liposarcoma	-- *	
Leiomyosarcoma	-- *	
MPNST	0.84 (0.06 – 11.66)	
Other#	3.98 (0.52 – 30.33)	
Fragmented Unplanned Excision		0.07
No	referent	
Yes	0.11 (0.01 – 1.19)	
Final Margin¶		0.99
R0	referent	
R1/R2	-- *	
Repeat Excision		0.99
Yes	referent	
No	-- *	

*Hazard ratios for these sub-groups were not defined.

#There were numerical problems when analyzing the histology using 6 categories, so DFSP was included with the Other category.

¶Given the low rate of R2 disease (N=1), data were analyzed in two groups: margin negative (R0) and margin positive (R1/R2).