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Research Report

Radiotherapy Outcomes and Prognostic Factors in Patients with Soft Tissue Sarcoma

Özgür Altmışdörtoğlu[1,2], Sema Rakici[1]

[1] Department of Radiation Oncology, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Türkiye
[2] Department of Radiation Oncology, Faculty of Medicine, Ankara University, Ankara, Türkiye

Corresponding Author: Sema Rakıcı

Address: Recep Tayyip Erdogan University, Faculty of Medicine, Rize, Türkiye

Tel: 05054028302

E-mail: sema.rakici@erdogan.edu.tr

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ORCID IDs of the authors:

Özgür Altmışdörtoğlu: 0000-0003-0683-544X

Sema Rakıcı: 0000-0002-5543-9761

Abstract

Objective: Soft tissue sarcomas are a rare type of cancer that arise from the soft tissues of the body. Treatment outcomes and prognostic factors in 86 patients with soft tissue sarcoma treated with postoperative or primary radiotherapy were retrospectively evaluated for prognosis assessment.

Materials and Methods: Patients with soft tissue sarcoma who received postoperative or primary RT were retrospectively evaluated. Parameters such as stage, location, histopathological type, tumor size, surgical features, chemotherapy status and radiotherapy dose/fractionation were evaluated in terms of prognostic value of the disease.

Results: The median age of the patients was 45 years (range, 18-80). The median dose of radiotherapy was 60 (range, 40-70) Gy at 1.8-2 Gy/fraction. The median follow-up period was 53 (range, 3-246 months) months. Five-year OS, DFS and LC were 68%, 61% and 76%, respectively. In univariate analysis, tumor size >10 cm (p=0.01), deep location (p=0.001), grade III-IV (p=0.0001), stage III (p=0.02) and (+) surgical margin (p=0.002) for OS, grade III-IV (p=0.0001), stage III (p=0. 030) and (+) surgical margin (p=0.012); for local control, tumor localization (extremity vs other) (p=0.028), grade III-IV (p=0.004), depth (p=0.035) and (+) surgical margin (p<0.0001) were found to be significant prognostic factors. In multivariate analysis, grade III-IV for OS and DFS (p=0.004 and p=0.001, respectively), surgical margin for local control (p=0.0001) and tumor localization (p=0.06), although not statistically significant, were found to be predictive prognostic factors.

Conclusion: In our study; high grade, positive surgical margins and tumor location outside the extremity were found to be the most important prognostic factors. These results are consistent with previous studies and should be taken into consideration in treatment planning.

Keywords: Grade, local control, prognostic factor, radiotherapy, soft tissue sarcoma.

Introduction

Soft tissue sarcomas (STS) are a rare type of cancer (<1% of all malignancies) that arise from the soft tissues of the body such as muscle, fat, blood vessels, nerves and tendons. These tumors can develop anywhere in the body and treatment usually involves surgery, chemotherapy (ChT) and radiotherapy (RT) (1). The median age is between 40 and 60 years, with a peak age of around 55 years (2). The male/female ratio is 0.8. Predisposing factors for STS include genetic syndromes such as Li-Fraumeni syndrome and neurofibromatosis type 1, previous radiation therapy and chronic lymphoedema. Exposure to certain viruses such as HIV or EBV can also increase the risk. Other factors include genetic mutations, exposure to chemicals, and a history of chronic inflammation in the affected tissue (3).

Surgical treatment is the gold standard for STS. The prognostic parameters affecting the clinical course are histological grade, status of surgical margins and tumor depth. RT has become an important part of the treatment of STS in the last 30 years and has led to a shift away from amputation. Adjuvant RT is used in cases with unfavorable prognostic features such as positive margins and large tumor size (4, 5).

In this study, we evaluated the effect of prognostic parameters on overall survival (OS), disease-free survival (DFS) and local control (LC) outcomes in patients who received adjuvant RT in a clinic within a certain time frame. The findings suggest that tumor size and deep location, high grade, positive surgical margins and stage III-STS have prognostic significance for OS and DFS in patients with STS. Further research and personalized treatment approaches may be required for optimal outcomes in this patient population.

Materials and Methods

General characteristics of the patients: Data from 86 patients who underwent RT for STS between January 1990 and January 2005 were retrospectively analyzed. All patients were restaged with AJCC 2010 staging system. Patient characteristics are summarized in Table 1.

Radiotherapy: RT was applied to patients with at least one of the following factors: postoperative positive surgical margins, tumor size greater than 5 cm, presence of metastatic lymph nodes, recurrence, and gross residual disease. RT was administered with a linear accelerator (LINAC) or Cobalt 60 (C0-60) device. RT application was performed with conventional or 3D conformal treatment methods. Until 1999, conventional planning was applied with Co-60; since then, 3D conformal RT planning has also been used.

While a safety margin of 5-7 cm on the vertical axis and at least 2-3 cm on the horizontal axis were given to the tumor lodge in 2-dimensional conventional planning for tumors located in the extremities, a safety margin of at least 1.5-2.0 cm was given to the primary tumor bed in other locations. For lesions located in the extremities, normal tissue was left from the medial or lateral parts depending on the tumor location to prevent possible lymphedema that may develop in the future. Patients who were planned to receive three-dimensional conformal treatment underwent planning tomography with appropriate simulation and treatment position. During planning, CTV was created by giving a margin of 3-6 cm and PTV was created by giving a margin of 1-2 cm to the CTV by using the preoperative imaging of the patients. In one patient with gross residue, PTV was created by giving similar margins to GTV as in other patients. The operation scar and drains were included in the field. After the first 50 Gy RT bolus was applied to the patients, the treatment was completed by reducing the area. The RT dose given to the patients was applied with a standard daily fraction dose of 1.8-2.0 Gy. Patients received RT in the dose range of 40-70 Gy. None of the patients who received treatment received brachytherapy.

Chemotherapy: All patients who received ChT received an anthracycline-based ChT regimen. Patients received ChT because of high grade, tumor diameter greater than 5 cm, relapse or other high risks.

Statistical Methods

The follow-up period of the patients was taken as the time between the end of RT and the last follow-up date for living patients and the time between the end of RT and death for deceased patients. SPSS version 16 was used for statistical calculations. OS, DFS and LC values were analyzed by Kaplan-Meier method, multivariate analyses were performed by Cox regression analysis and univariate analyses were performed by log-rank test. Statistical significance $p<0.05$ was accepted.

Ethics statement: TR Index Journal Evaluation criteria have been updated to be implemented in 2020, and the articles related to the ethics committee permission required in scientific research have been detailed. The documents and information process requested for studies requiring ethics committee approval, which is stated under the title of ethical rules, has become mandatory for publications starting in 2020 (6). Retrospective research data derived from studies prior to 2020, does not require ethical committee approval.

Results

Patient characteristics are summarized in Table 1. The age range of the patients was 18-80 years with a median 45. The most common site of the tumor is the extremity. The most common initial complaint was painless mass and the most common radiological method used in the diagnosis was magnetic resonance imaging. The most common surgical procedure was wide local excision, which was performed in 57% of all cases. The most common histopathological subgroup detected in the patients was ‘malignant fibrous histiocytoma’ that constituted 27% of all cases. The median dose of RT was 60 Gy, and RT was started on a median of 81 days after diagnosis. Adjuvant ChT was administered in 49 (57%) of all cases. Adjuvant ChT information is summarized in Table 2.

Table 1. General characteristics of the patients, tumors and treatments.

Table 2. Chemotherapy administration status and chemotherapy schemes of the patients.

Histological grade was the most important prognostic factor for OS and DFS and was found to be significant in both univariate analysis ($p=0.0001$ for both parameters) and multivariate analysis ($p=0.004$ and $p=0.001$, respectively).

In terms of LC, histological grade was not found to be a significant prognostic factor in multivariate analysis, but in univariate analysis ($p=0.004$).

Superficial or deep location of the tumor was found to be significant for OS, DFS and LC in univariate analysis and was the second most important prognostic parameter after histological grade only for OS in multivariate analysis; OS, DFS and LC in univariate analyses, and the most important prognostic factor for LC in multivariate analysis ($p=0.0001$).

Limb location was found to be significant in terms of LC in univariate analysis ($p=0.028$), while it was close to significance in multivariate analysis ($p=0.06$).

Overall Survival

A median of 86 patients were followed up for a median of 53 months (range, 3-246 months) after RT. At the end of the study, 57 (66.3%) patients were alive and 29 (33.7%) were lost. DFS was 61% and LC rate was 76% in the patient group. 5-year OS was 68%. The OS curve is shown in Figure 1

In univariate analysis, tumor diameter >10 cm (p=0.01), deep tumor location (p=0.001), grade III-IV (p=0.0001), stage III (p=0.02) and positive surgical margins (p=0.02) were found to be statistically significant negative prognostic factors for overall survival. No significant correlation was found between age, gender, presenting complaint, type of surgery, RT dose, adjuvant ChT, recurrence, time between operation and RT and prognosis. The results of univariate analysis are summarized in Table 3 and Figure 1.

Table 3. Prognostic factors in univariate analysis for overall survival.

Figure 1. Prognostic factors for overall survival according to univariate analysis results.

In multivariate analysis, high grade and deep tumor location were found to be negative prognostic factors for overall survival. Grade I –II vs. III – IV (HR: 3.03, 95% CI: 1.142-8.036, p=0.004) and superficial vs. deep location (HR: 6.45, 95% CI: 1.182-22.900, p=0. 026).

Disease-Free Survival

During the follow-up period, 46 out of 86 patients were in remission (53.5%) and 5-year DFS was found to be 61%. In univariate analysis, being grade III (p=0.0001), being stage III (p=0.030), having positive surgical margins (p=0.012) and having deep tumor localization (p=0.030) were found to be significant for DFS. DFS and the parameters examined by univariate analysis are given in Table 4 and Figure 2.

In multivariate analysis, the only prognostic factor for DFS was found to be “grade”. Grade I –II vs. grade III – IV (HR: 7.18, 95% CI: 2.44 – 21.14, p=0.001).

Table 4. Prognostic factors in univariate analysis for disease-free survival.

Figure 2. Prognostic factors for disease-free survival according to univariate analysis results.

Local control: The 5-year LC rate in patients was found to be 76%. In terms of LC, location (p=0.028), depth (p=0.035), grade (p=0.004) and surgical margin status (p<0.0001) were found to be statistically significant in univariate analysis. In multivariate analysis, surgical margin (negative vs. positive surgical margin) was found to be the most important prognostic factor (HR: 13.62, 95% CI: 3.84- 48.22, p<0.001) (p=0.0001). The location of the tumor in the extremity or outside the extremity was found to be a prognostic factor close to statistical significance (HR: 0.30, 95% CI: 0.86 – 1.054, p= 0.06). The OS and disease-free survival curves are shown in Figure 3.

Figure 3. Overall survival (1a) and disease-free survival (1b) graphs.

Follow-up: Local relapse developed in 20 out of 86 patients; 13 of these patients had only local relapse and 7 had both local and distant metastases, 3 of the patients who developed only local relapse received only local surgical excision and 4 patients received local excision followed by ChT. 3 of the patients who developed both local and distant relapse received ChT, 1 patient received local excision+ChT and 3 patients did not receive treatment due to poor general condition. During the follow-up period, 54 cases were non-metastatic (61.6%). Distant metastases were lung metastases in 22 cases (25.6%), liver metastases in 1 case, bone metastases in 2 cases (2.3%), and widespread multiple metastases in 7 cases (8.1%).

Discussion

Sarcomas are rare tumors, representing only 0.8% of new cancers in the United States (7). The most common STS histopathological type is malignant fibrous histiosarcoma (8). Sarcomas can occur in people of all ages but are more commonly diagnosed in adults. There may be differences in the prevalence of STS between men and women in terms of gender ratios (slightly higher male-to-male ratios overall), but more research is needed to fully understand

these patterns on a global scale. In our study, the female-to-male ratios were 47.7% and 52.3%, respectively. The incidence of STS typically peaks in middle age, with the highest prevalence in individuals between the ages of 50 and 70 (9). In our study, 36% were under the age of 40, 40% were between the ages of 40-59, and 24% were over the age of 60.

STS encompass a diverse group of more than 50 histopathologic subtypes, including but not limited to leiomyosarcoma, liposarcoma, and synovial sarcoma. Each subtype has distinct characteristics, growth patterns, and treatment options, making accurate histopathologic diagnosis crucial for the appropriate management of patients with STS (10). In our study, the first four most common types were malignant fibrous histiocytoma, liposarcoma, fibrosarcoma and synovial sarcoma.

The data in the literature suggest that achieving negative surgical margins is crucial to improving LC in extremity STS. This highlights the importance of careful preoperative planning and precise surgical techniques to optimize outcomes in patients undergoing surgery for STS (11). In the study by Patrick W. O'Donnell et al., 5-year local recurrence-free and cause-specific survival rates for patients with positive surgical margins were 63.4% and 59.2%, respectively. This highlights the importance of considering the impact of surgery and positive surgical margins on both survival outcomes and LC in patients with STS (12). In our study, surgical margin positivity was found to be a negative prognostic factor for OS and DFS.

The main treatment for STS is curative surgical excision; the tumor and biopsy tracts should be removed with negative normal tissue margins (13). Although STS are usually treated with amputation and wide excision, limb-sparing procedures have not been shown to have a negative impact on local recurrence or outcome as long as the tumor is completely removed. (8). Compartment excision is no longer generally recommended and wide local excision with a margin of normal tissue around the tumor is the current surgical goal. The feasibility of limb-sparing resection depends on the complications associated with removal of surrounding structures (7).

In STS, ChT is recommended for patients with high-grade sarcomas. It may also be used as primary treatment for high-grade tumors or as an adjuvant following surgery to help prevent recurrence. High-risk patients with large, deep tumors or tumors in critical areas are likely to benefit from neoadjuvant ChT. There is no convincing evidence that adjuvant ChT improves overall survival. A meta-analysis of patients with STS treated with adjuvant doxorubicin-based ChT showed no significant improvement in survival. (14). Adjuvant ChT is still not the standard of care for resected primary STS. Neoadjuvant ChT is effective in the treatment of rhabdomyosarcoma and has high response rates. The role of neoadjuvant ChT for other histologic subtypes is controversial. Neoadjuvant ChT can guide the response and prognosis of the STS. However, neoadjuvant ChT has side effects that include the risk of triggering progression. Doxorubicin and ifosfamide are commonly used by ChT agents. Data on the use of neoadjuvant ChT come from small retrospective series and a small number of randomized controlled trials (7).

RT has been shown to improve LC rates in high-risk STS (15). It reduces the risk of recurrence and increases the likelihood of successful treatment. Neoadjuvant and adjuvant RT significantly reduces the risk of local recurrence and improves OS in patients with extremity STS (15). Timing of RT influences outcomes, highlighting the need for individualized treatment plans. A delay of 4 months or more in postoperative radiation is associated with poorer LC, highlighting the importance of timely administration for improved outcomes (16). In our study, RT dose or RT delay was not found to be an effective factor on OS and LC.

Limitations of the study include the comparison with a patient group that did not receive RT, the use of older RT methods, and its retrospective nature. Current RT techniques utilize more advanced technologies, such as IMRT and VMAT, which create more homogeneous and conformal planes (17). Nevertheless, our study is important because it presents data from patients treated with previously used RT techniques.

Radiation may be an effective treatment to reduce local recurrence of STS (15). The recurrence rate is low in patients with low-grade sarcoma (18), whereas limb-sparing surgery alone may have a higher recurrence rate. Adjuvant RT has not been shown to have an effect on survival (7). Radiation therapy is recommended for high-grade lesions, low-grade lesions of >5 cm, or those with positive margins (7). Patients who undergo re-excision should also receive adjuvant RT. Preoperative radiation may allow for more conservative surgical management. It has been noted that preoperative RT may increase wound complications. In deciding between preoperative and postoperative RT, the type of surgical procedure, wound closure and tension, width of the surgical bed, the possibility of achieving negative margins, and the extent of STS should be considered. However, the advantages and disadvantages of RT should be considered in each case.

Conclusion

In STS patients who underwent RT, histological grading maintained its significance in multivariate analysis for both OS and DFS, while surgical margin negativity maintained its significance in univariate analysis for all parameters but was the most important prognostic factor in multivariate analysis for LC only.

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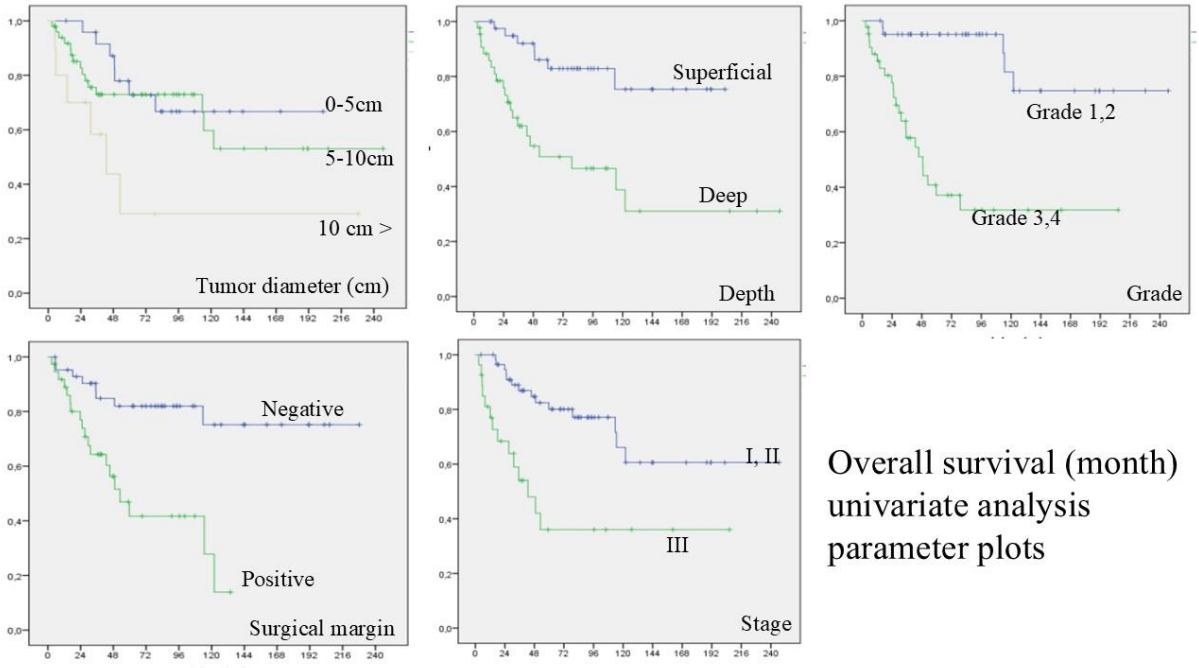

Figure 1. Prognostic factors for overall survival according to univariate analysis results.

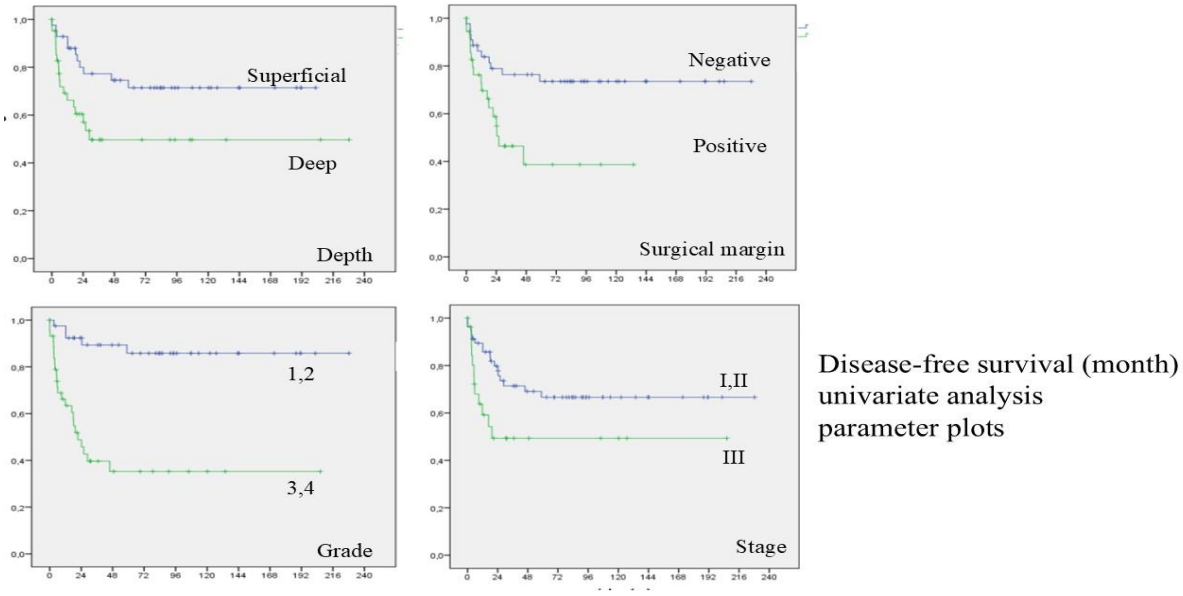

Figure 2. Prognostic factors for disease-free survival according to univariate analysis results.

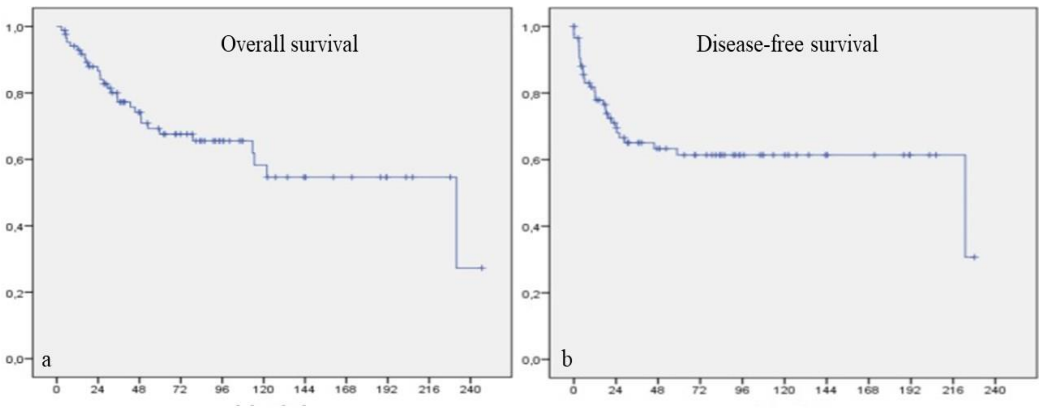

Figure 3. Overall survival (1a) and disease-free survival (1b) graphs.

Table 1. General characteristics of the patients, tumors and treatments.

Variables	**n**	**%**
Gender		
Female	41	47.7
Male	45	52.3
Age distribution		
<40 years	31	36
40 -59 years	34	40
≥60 years	21	24
Presenting complaint		
Mass	63	73.3
Pain	10	11.6
Mass + pain	9	10.5
Neurological symptom	2	2.3
No complaint	2	2.3
Radiological method used in the diagnosis		
Computed tomography (CT)	24	27.9
Magnetic resonance imaging (MRI)	35	40.7
CT+MRI	12	14.0
Ultrasonography	5	5.8
Direct graph	3	3.5
No imaging	7	8.1
Location		
Extremity	68	79.1
Head and neck	1	1.2
Trunk	13	15.1
Retroperitoneum	4	4.7
Grade		
I	7	8.1
II	42	48.8
III	35	40.7
IV	2	2.3

Tumor Depth		
Deep	44	52.3
Superficial	42	47.7
Tumor diameter		
<5 cm	26	30.2
5-10 cm	50	58.1
≥10 cm	10	11.6
Histological subgroup		
Malignant fibrous histiocytoma	23	26.7
Liposarcoma	17	19.8
Fibrosarcoma	10	11.6
Synovial sarcoma	12	14.0
Malignant schwannoma	9	10.5
Rhabdomyosarcoma	1	1.2
Leiomyosarcoma	8	9.3
Malignant mesenchymal tumor	6	7
Stage (AJCC 2010)		
Stage I	9	10.5
Stage II	53	61.6
Stage III	24	27.9
Surgical Type		
Wide excision	49	57.0
Intralesional excision	12	14.0
Marginal excision	24	27.9
No operation	1	1.2
Surgical margin status		
Negative	44	51.2
Positive	30	34.9
Close	7	8.1
Unknown	4	4.7
Gross residual	1	1.2
Chemotherapy administration		
Adjuvant	45	52.0
Neo adjuvant	2	2.3
RT alone concomitant chemotherapy	2	2.3
No chemotherapy	37	43.0
Radiotherapy		
Adjuvant	74	86.0
Primary	1	1.2
Relapse	11	12.8
Radiotherapy dose		
< 60 Gy	22	26
≥ 60 Gy	64	74

Table 2. Chemotherapy administration status and chemotherapy schemes of the patients.

Chemotherapy treatment		
Adjuvant	45	52.0
Neoadjuvant	2	2.3
Concurrent with RT	2	2.3
Chemotherapy regime		
Adriamycin concurrent with RT	2	2.3
Ifosfamide mesna+adriamycin (IMA)	41	47.5
Etoposide+vincristine+adriamycin+cytoxan (EVAC)	3	3.5
Ifosfamide + etoposide + vincristine	3	3.5

Table 3. Prognostic factors in univariate analysis for overall survival.

Prognostic Factor **5-year Overall Survival**	**%**	***p* value**
Tumor diameter		
0-5 cm	69.2	0.01*
5-9.99 cm	70.0	
10cm	40.0	
Deept		
Superficial	81.0	0.001*
Deep	52.3	
Grade		
Grade I-2	88.1	0.0001*
Grade 3-4	45.5	
Stage		
Stage I-II	74.6	0.02*
Stage III	48.1	
Surgical margin		
Negative	79.5	0.002*
Positive	48.6	
Other Age, gender, presenting complaint Surgery type, radiotherapy dose Adjuvant chemotherapy Presenting with relapse Time between operation and radiotherapy time		*p*>0.05

* *p*<0.05 statistically significant.

Table 4. Prognostic factors in univariate analysis for disease-free survival.

Prognostic Factor	**5-year disease-free survival**	***p* value**
Depth		
Superficial	%73.8	
Deep	%56.8	0.030*
Grade		
Grade I-II	%85.7	
Grade III-IV	%45.5	0.0001*
Stage		
Stage I-II	%69.5	
Stage III	%55.6	0.030*
Surgical margin		
Negative	%75.0	
Positive	%54.1	0.012*
Other: Age, gender, presenting complaint, tumor diameter, surgery type, radiotherapy dose, adjuvant chemotherapy, presenting with recurrence, duration between surgery and radiotherapy, location	*p*>0.05	

* *p*<0.05 statistically significant.