ANALYSIS

24(105), September - October, 2020

ISSN 2321–7359 EISSN 2321–7367

Medical Science

Head and Neck Synovial Sarcoma: Egyptian National Cancer Institute Experience

Hala Aziz Shokralla[1]✉, **Ahmed Elsayed Fathalla**[2]

[1]Assistant Professor of Medical Oncology-National Cancer Institute-Cairo University-Egypt; Email: Halaaziz2001@Yahoo.Com
[2]Assistant Professor of Surgical Oncology-National Cancer Institute-Cairo University-Egypt; Email: drasf1975@gmail.com

✉**Corresponding author**
Assistant Professor of Medical Oncology-National Cancer Institute-Cairo University,
Egypt
Email: Halaaziz2001@Yahoo.Com

Article History
Received: 27 June 2020
Reviewed: 28/June/2020 *to* 31/July/2020
Accepted: 31 July 2020
E-publication: 06 August 2020
P-Publication: September - October 2020

Citation
Hala Aziz Shokralla, Ahmed Elsayed Fathalla. Head and Neck Synovial Sarcoma: Egyptian National Cancer Institute Experience. *Medical Science*, 2020, 24(105), 3121-3127

ABSTRACT

Background: Head and neck synovial sarcoma (HNSS) are rare types of sarcomas of uncertain etiology. They appear predominantly in young adults, with a peak incidence in the third decade. They are considered as a high-grade sarcoma with poor prognosis. *Aims:* to study the clinicopathological features of all cases with HNSS, pathological subtypes, management protocols & the outcome of such treatments as regard progression-free survival (PFS) & overall survival (OS). *Materials & Methods*: a retrospective analysis of all cases presented to National Cancer Institute-Cairo University from January 2011 until December 2019. 16 cases were included. Data collected then analyzed. *Results:* Mean age was 30.6 years with male to female ratio of 1.3:1. Anatomically; 5 cases were in the neck

soft tissues, 3 cases were in the cheek, 2 cases were in each of hypopharynx, oropharynx & temporal regions, one case in thyroid gland and submandibular gland. Mean tumor size was 7.38 cm. Surgical resection was done in all patients; postoperatively, 4 cases (25%) <had R0 margins with no further treatment; twelve cases had (R1/R2) resection. Five patients (~31%) developed metastasis and 3 patients (~19%) developed both local and distant metastases; lungs were commonest site (~94%). Median follow-up was 57.2 months (range, 6.76–100 months). Overall survival at 1, 3, and 5 years were 95.1%, 71.4% & 42.9% respectively while the corresponding PFS were 68.6%, 30.7% & 16%. *Conclusion:* Surgery is the primary treatment for localized tumors. Radiotherapy/chemotherapy is options. Initial tumor size & margins of resection was the main predictive of survival.

Keywords: synovial sarcoma, surgical resection, localized tumors, chemotherapy

1. INTRODUCTION

Head and neck synovial sarcoma (HNSS) were first reported by Jernstorm in 1954. "Synovial" literally means that these tumors show a similar feature to the synovium on microscopy as was thought. However, further studies revealed that the origin of these tumors is from a pluripotent mesenchymal cell and not from any synovial structures, although we still use this original mis-nomenclature (Crowson et al., 2015). HNSS accounts for ~ 2.5–3.5% of all head and neck (HN) sarcomas. It appears predominantly in young &middle-aged adult males between age of 15 and 40 years with a peak incidence in the third decade. It is characterized by a very high incidence of early regional nodal (Al-Daraji et al., 2009). It can arise anywhere in HN region, although upper aerodigestive tract and soft tissues are commonest. Typically, it presents by slowly growing painless neck lump that with or without dysphagia, odynophagia or hoarseness of voice (Sturgis & Potter, 2003).

Etiology remains unclear; it can rarely arise in a previously irradiated field. Histologically, there are two major subtypes (biphasic or monophasic) based on its components; whether spindle cells only or both spindle and epithelial cells. Other rarer subtypes include (monophasic epithelial, poorly differentiated, calcifying/ossifying, and myxoid types) (Carrillo et al., 1992). It is generally considered a high-grade sarcoma with poor prognosis. Major prognostic factors include size, histological subtypes (monophasic or biphasic), site, bone or neurovascular invasion, margin status, stage, age and gender. Estimated 5-years overall survival (OS) rate ranging from 50% to 60% and 5-years disease free survival (DFS) rate ranging from 40% to 60% (Harb et al., 2007; Mallen-St Clair et al., 2016).

Magnetic resonance imaging (MRI) is the ideal image for diagnosis and staging. Differential diagnosis is extremely wide; myoepithelial carcinoma, malignant peripheral nerve sheath tumor, leiomyosarcoma, solitary fibrous tumor, dermatofibrosarcoma protuberans, rhabdomyo sarcoma orepithelioid sarcoma (Ferrari et al., 2004). Treatment is multimodal, including surgery, radiotherapy (RT) and/or chemotherapy (CTH) with a mandatory long term follow up period. The Standard management of primary localized disease is wide surgical resection with clear margins (R0) if feasible followed by adjuvant RT in patients with high-risk disease (grade III, deeplesions, and size more than 5 cm) (Shi et al., 2013; Spillane et al., 2000). Chemotherapy is considered in patients with advanced, recurrent or metastatic cases (Sleijfer et al., 2010).

Aim of work

The aim of our study was to investigate the impact of traditional clinical and pathological factors and to assess survival in a series of unselected patients with HNSS from single institution practice data in order to identify prognostic determinants.

2. MATERIAL AND METHODS

Patients

This retrospective study included all patients diagnosed with HNSS, treated at the Department of Surgical Oncology–National Cancer Institute-Cairo University-Egypt during 9 years from January 2010 until December 2019. 16 cases were included. Data was collected including demographic features (age and sex), tumor characters (type, grade, stage according to AJCC, primary or recurrent), surgical morbidities & treatment received; chemotherapy, radiation or both and the outcomes.

Chemotherapy was considered for locally advanced disease as neoadjuvant (doxorubicin 60 mg/m2 IV push D1 and ifosfamide 3000 mg/m2 D1,2,3 with mesna D1,2;3 repeat every 21 days for 4 to 6 cycles) was and when metastasize.

Radiotherapy was considered as adjuvant post operatively in all primarily operated cases as 50 Gray/25 fraction (50 Gy/25Fx), 60 Gy/30Fx or 66 Gy/33Fx in (~81%) of cases; doses differ according to the anatomical site of the primary tumor and its grade. Chemoradiotherapy was received as a definitive primary treatment in oropharyngeal and hypopharyngeal SS.

Statistical analysis

Treatment failure patterns were classified into local recurrence and distant metastasis. Primary endpoint of this study was to evaluate the prognostic role of all clinical and pathological parameters in HNSS. Overall survival (OS) is the time from random assignment to the date of death due to any cause, or to the date of censoring at the last time the subject was known to be alive (Cheema et al., 2013), while disease free survival (DFS) the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients who are lost to follow-up (Soria et al., 2010).

Survival distribution was estimated by the Kaplan—Meyer method. Significant differences in probability of surviving between the strata were evaluated by log-rank test. A significant level of 0.05 was chosen to assess the statistical significance. Ethical clearance for the conduction of this study was obtained from our institute ethical committee.

3. RESULTS

Sixteen patients were included with non-metastatic HNSS. Ages ranged from 13 to 63 years (median; 28years). Nine patients (~56 %) were males with male to female ratio of 1.3:1. Lesions were distributed anatomically as; 5 in the neck soft tissues, 3 in the cheek, 2 in the hypopharynx, 2 in the oropharynx, 2 in the temporal region, 1 in the thyroid and 1 in the parotid gland; sizes range from 4 -15 cm (mean size 7.38 cm). The staging system most often used for synovial sarcoma is the American Joint Committee on Cancer (AJCC) of soft tissue sarcoma (STS). According to this AJCC staging criteria; in our cohort T1 tumors (< 5cm) were (3 cases, ~19%) T2 tumors (5-10cm) were (6 cases, 37.5%) and T3 tumors (10-15cm) were (7 cases,~ 44%).There were no T4 (>15cm) lesions in this study (table 1).

Table 1 pathological character in our study (16 cases, 100%)

Pathological types	Monophasic Biphasic Ossifying	11 cases, 69% 4 cases, 25% 1 case, 6%
Margins	Negative Close Positive (R1)	4 cases, 25% 6 cases, 37.5% 6 cases, 37.5%
Grade	I II III	1 case, 6% 13 case, 81% 2 cases, 13%
Stage	I II III a III b	1 case, 6% 3 cases, 19% 5 cases, 31% 7 cases, 44%
Treatment	Surgery Adjuvant radiation Neoadjuvant chemotherapy Chemo-radiotherapy	 12 cases ,75% 12 cases ,75% 2 cases ,13% 2 cases,13%

The standard treatment is surgical resection; in our study, it was feasible as a primary treatment in 12 patients (75%). In two patients (oropharyngeal and other with hypopharyngeal SS), concomitant CTH/RTH was received primarily as a definitive primary treatment and salvage total laryngo-pharyngectomy with gastric pull-up was done later for residual. Another two patients (12.5%) with locally advanced disease invading the skin of the neck received neoadjuvant CTH (doxorubicin and ifosfamide). Postoperatively, 4 patients (25%) had adequate surgical margins, and no further treatment was given. Twelve patients (75%) had close margins (R1 resection); all of them received adjuvant radiation. Twelve patients (75%) suffered disease failure; four cases (25%) developed local recurrence; five patients (~31%) developed distant metastasis and 3 patients (~19%) developed both local and distant metastases (figure1-4).

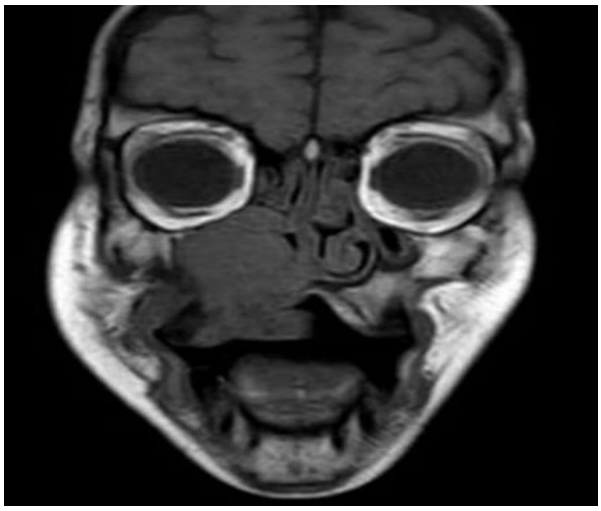


Figure 1 MRI maxillofacial (coronal view) of patient with right maxillary synovial sarcoma extending intranasal & destroying the infraorbital wall.

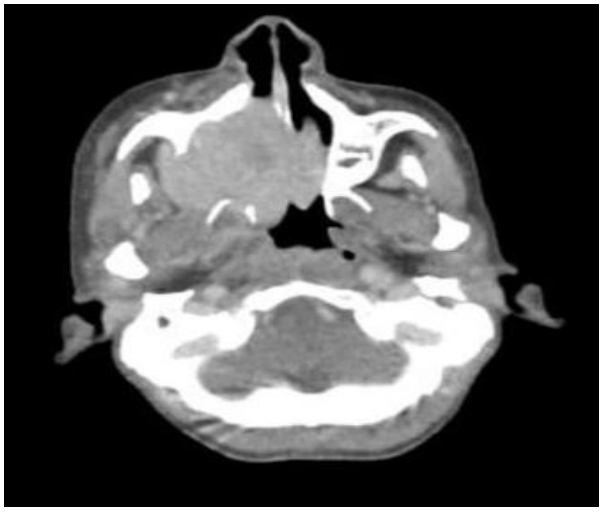


Figure 2 CT scan (axial view) of patient with right maxillary synovial sarcoma extending intranasal & destroying the infraorbital wall

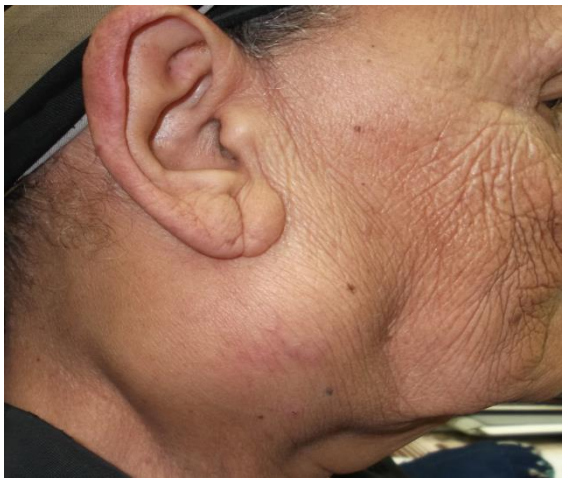


Figure 3 Parapharyngeal synovial sarcoma involving parotid gland.

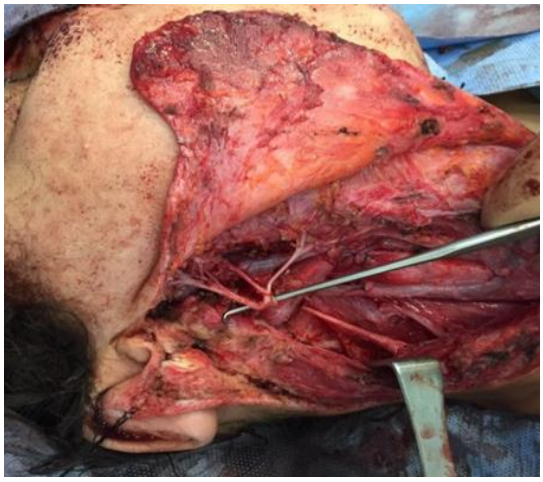
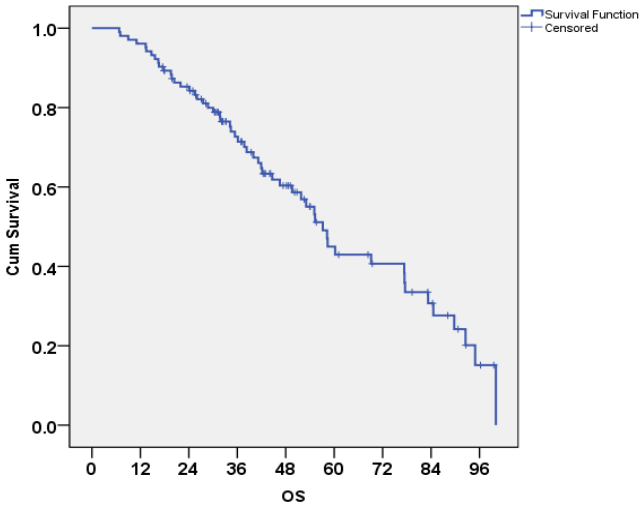
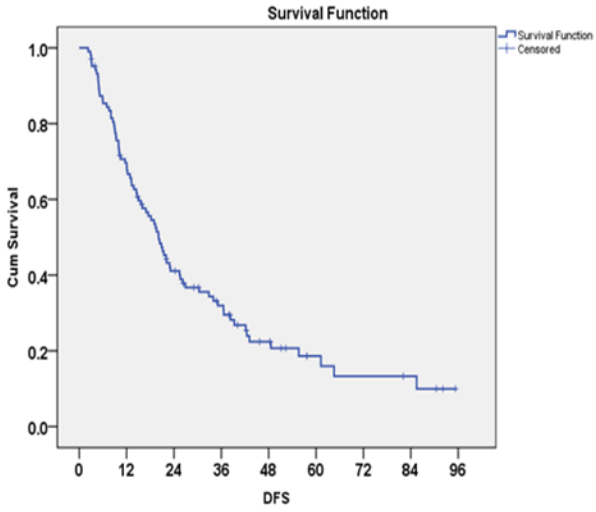


Figure 4 Parapharyngeal synovial sarcoma involving parotid gland.

Sites of distant metastases were the lungs (~94%), bones (~13%), peritoneum (~6%), and breast (~6%). Treatment of local recurrence depended on its site. Four patients underwent re-resection followed by RTH (if was not given) and /or chemotherapy (ifosfamide /doxorubicin). Time to local recurrence varied from 2.87 to 95.32 months, with a median of 42.2 months. The median follow-up time was 57.2 months (range, 6.76–100 months). Overall survival rates at 1, 3, and 5 years were 95.1%, 71.4%, and 42.9%, respectively. The corresponding DFS rates were 68.6%, 30.7%, and 16%, respectively (graph 1& 2).



Graph 1 Overall survival



Graph 2 Disease free survival of all cases

4. DISCUSSION

Worldwide, HNSS constitutes 5-10% of synovial sarcomas and~ 2-5% of all STS. It predominates in young and middle-aged adults. It can arise anywhere HN region mainly upper aerodigestive tract. Etiology remains unclear had history of RT for brain tumor (Zagars et al., 2003). As regard histology, there are two major subtypes (biphasic & monophasic); the monophasic is more common; matching with our reported data, 11 patients (~69%) were recorded (Bergh et al., 1999). It is considered a high-grade sarcoma with a poor prognosis. The expected 5-years OS ranges between 50% & 60%; while the 5-years DFS ranges between 40% & 60%. Our 5-years OS was 42.9% and 5-years DFS was 41.6% which is slightly lower than those found in most of literatures (Al-Daraji et al., 2009). Management of HNSS is a multimodal approach, involving surgery, radiation and/orchemotherapy with a long-term follow-up. The standard management of a primary localized disease is still wide surgical resection followed by radiation in high-risk disease (Grade III, deeply located, and > 5 cm). Surgical resection of the primary non-metastatic HNSS was performed to 14 patients (87.5%) except two cases with oropharyngeal & hypopharyngeal SS who was treated with definitive CCRTH (Wushou & Miao, 2015).

After review of our pathology reports, four patients (25%) had adequate surgical margins, and no further treatment was given. Twelve patients (75%) had close margins (R1 resection) (< 0.5cm) & only ten received adjuvant RTH; the other two patients (~13%) had received combined neoadjuvant CTH/ RTH. Surgical resection in the region of the HN carries a very high risk of nerve & vascular injury; only 25 % of our cases were surgically cleared of the disease primarily with no further treatment (Al-Daraji et al., 2009; Wushou & Miao, 2015). Reconstruction of post-operative defects (skin, soft tissue or bone) can be done either by local rotational flaps or remote free tissue transfers. Surprisingly, in our study, despite the majority (13 patients, ~81%) were >5cm, only two cases, ~13%) needed a mode of reconstruction for coverage (one needed pectoralis major myo-cutaneous flap for floor of mouth defect & other needed deltopectoral flap for coverage of a lower neck skin loss). Free flaps are now mandatory following salvage surgery, although was not needed in this cohort (Bukachevsky et al., 1992).

Radiation can be administered either as primary definitive treatmentor adjuvant treatment. Newer radiation techniques such as intra-operative radiotherapy (IORT) and intensity-modulated radiotherapy (IMRT) have led to improvement of outcomes in patients with HNSS. In our work, adjuvant RT was given to twelve patients (75%) as 50 Gray/25 fraction (50 Gy/25Fx), 60 Gy/30Fx or 66 Gy/33Fx in (~81%) of cases; doses differ according to the anatomical site of the primary tumor and its grade (Zagars et al., 2003). Chemotherapy is considered in both the neoadjuvant and adjuvant settings for patients with advanced HNSS. In our study, neo-adjuvant CTH was given for two patients (~13%) preoperatively, another two patients received adjuvant postoperative CTH with R1 positive margins due to irresectability All cases received chemotherapy once developed distant metastasis; in form of ifosfamide /doxorubicin (Vlenterie et al., 2016; Gopalakrishnan et al., 2017).

Our analysis showed that tumor size <5 cm (T1) vs. >10 cm (T3, T4) was associated with improved OS (44.4% vs. 31% at 5 years, respectively; p = 0.03). Adjuvant RTH improves significantly overall survival (52.5% vs. 21.5% at 5 years, respectively; p < 0.001). Similarly, patients with tumors <5 cm had better DFS than larger tumors >10 cm (36.3% vs 12.8%, and 14.5% vs 3.2% at 3 and 5 years respectively; p = 0.005). Surgical safety margin affectsDFS, as negative margin (RO) associated with improved DFS compared to positive margins (R1) (39.2% vs. 24.2% at 3years, respectively; of borderline significance p = 0.31) in concordance with Mallen-St Clair et al., 2016. Adjuvant RTH also improve disease-free survival (37.7% vs. 9.4% at 3 years, respectively; p = 0.002). Patient's age and gender, histopathological subtype (biphasic or monophasic) and grade, and use of chemotherapy had not significant influence on did not significantly influence OS; as matching with results of Crowson et al. and Harb et al. (Crowson et al., 2015; Harb et al., 2007) or on DFS as previously published (Mallen-St Clair et al., 2016; Zagars et al., 2003; Gopalakrishnan et al., 2017).

5. CONCLUSION

Despite the retrospective character, the treatment's heterogeneity and the small sample size, our study confirmed the known independent prognostic factors in an unselected population from single institution and underlined the role of surgery as primary treatment for localized tumors. Tumor size & margins of resection was the main predictive of survival. These results prompted us to do further confirmatory investigations.

Funding: This research received no external funding.

Conflict of Interest: We declare that we have no conflict of interest.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of National Cancer Institute-Cairo University.

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

REFERENCES AND NOTES

1. Al-Daraji W, Lasota J, Foss R, Miettinen M. Synovial sarcoma involving the head: analysis of 36 cases with predilection to the parotid and temporal regions. Am J of Surg Pathol. 2009; 33(10):1494–1503.
2. Al-DarajiW, Lasota J, Foss R, Miettinen M.Synovial sarcoma involving the head: analysis of 36 cases with predilection to the parotid and temporal regions. Am JSurgPathol. 2009;33(10):1494–1503.
3. Bergh P, Meis-Kindblom JM, Gherlinzoni F, et al. Synovial sarcoma. Identification of low and high-risk groups. Cancer. 1999; 85(12): 2596–2607.
4. Bukachevsky RP, Pincus RL, Shechtman FG, Sarti E, Chodosh P. Synovial sarcoma of the head and neck. Head Neck. 1992; 14(1): 44–48.
5. Carrillo R, Rodriguez-PeraltoJL, Batsakis JG. Synovial sarcomas of the head and neck. AnnOtol Rhinol Laryngol. 1992; 101(4): 367–370.
6. Cheema P, Burkes R. Overall survival should be the primary endpoint in clinical trials for advanced non-small cell lung cancer. Curr Oncol. 2013; 20:2.
7. Crowson MG, Lalich I, Keeney MG, Garcia JJ, Price DL. Clinicopathologic factors and adjuvant treatment effects on survival in adult head and neck synovial cell sarcoma. Head Neck. 2015; 37(3): 375–380.
8. Ferrari A, Gronchi A, Casanova M, etal. Synovial sarcoma: a retrospective analysis of 271 patients of all ages treated at a single institution. Cancer. 2004; 101(3): 627–634.
9. Gopalakrishnan V, Amini B, Wagner MJ, et al. Sarcoma of the Head and Neck: A Single Institution Review. Sarcoma. 2017; 2016752.
10. Harb WJ, Luna MA, Patel SR, et al. Survival in patients with synovial sarcoma of the head and neck: association with tumor location, size, and extension. Head Neck. 2007; 29(8):731–740.
11. Mallen-St ClairJ, Arshi A Abemayor E, St John M. Factors associated with survival in patients with synovial cell sarcoma of the head and neck: An analysis of 167 cases using the SEER (Surveillance, Epidemiology, and End Results) database. JAMA Otolaryngol - Head Neck Surg. 2016;142(6):576–583.
12. Shi W, Indelicato DJ, MorrisCG, Scarborough MT, GibbsCP and Zlotecki RA. Long-term treatment outcomes for patients with synovial sarcoma: a 40-year experience at the University of Florida. Am JClin oncol. 2013;36(1), 83-88.
13. Sleijfer S, Ouali M, van Glabbeke M, et al. Prognostic and predictive factors for outcome to firstline ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: An exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer. 2010; 46:72-83.
14. Soria JC, Massard C, Le Chevalier T. (2010). Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? Ann Oncol. 2010;21(12), 2324-2332.
15. Spillane AJ, A'Hern R, Judson IR, Fisher C, Thomas JM. Synovial sarcoma: aclinicopathologic, staging, and prognostic assessment. J Clin Oncol. 2000;18:3794–803.
16. Sturgis EM, Potter BO.Sarcomas of the head and neck region. Curr Opin Oncol. 2003; 15 (3):239–252.
17. Vlenterie M, Litière S, RizzoE, et al. Outcome of chemotherapy in advanced synovial sarcoma patients: Review of 15 clinical trials from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group; setting a new landmark for studies in this entity. Eur J Cancer. 2016;58, 62-72.
18. Wushou A, Miao XC. Tumor size predicts prognosis of head and neck synovial cell sarcoma. OncolLett. 2015; 9(1): 381–386.
19. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer. 2003; 97:2530.
20. Zagars GK, Ballo MT, Pisters PWT, et al. Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: a retrospective comparative evaluation of disease outcome. Int J Radiat Oncol Biol Phys. 2003;56:482-488.