

Head and Neck Tumors: Management of Primary Undifferentiated Pleomorphic Sarcoma

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Abstract

Introduction:

Sarcomas account for 1% of all tumors originated in the head and neck regions in adults. They constitute a heterogeneous group of tumors of mesenchymal origin with multiple histological variants. The undifferentiated pleomorphic sarcoma (UPS) subtype is the most frequent variant with an incidence range of 2.7-38%.

Materials and Methods:

This retrospective case series was conducted on 11 patients who were diagnosed with UPS and treated in our institution in the last 11 years.

Results:

According to the results, 26.8% of the sarcomas corresponded to UPS variant. Out of 11 patients, 5 cases were female. The median age of the participants was 58 years (range: 18-74 years). Seven and four patients were T1b and T2b, respectively. Ten patients had no metastasis at the moment of diagnosis. Six patients were categorized as intermediate-grade, and the remaining (n=5) were classified as high-grade. The most frequent location was the scalp (n=3). In the patients undergoing surgery, the mean follow-up duration was 52 months. Disease-free survival (DFS) rates were obtained at 70%, 50%, and 50% in the 1st, 3rd, and 5th years, respectively, with the mean DFS of 36 months. In addition, the overall survival rates in the 1st, 3rd, and 5th years were 100%, 100%, and 83%, respectively.

Conclusion:

The UPS represented the most common histological subtype in our series. They tend to be intermediate or high-grade tumors. An acceptable global survival rate justifies surgical treatment as the main therapeutic tool.

Keywords:

Head, Neck, Neoplasms, Sarcomas, Undifferentiated pleomorphic sarcomas.

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Introduction

Sarcomas represent approximately 1% of the tumors in adult population (1,2). Approximately, 80% of these tumors originate in the soft tissues, and the remaining (20%) develop in the bone and cartilage (3). Soft tissue sarcomas mostly affect the adult population (80%) (4). Based on the evidence, 5-15% of all sarcomas in adults are found on the neck and head.

Sarcomas constitute a heterogeneous group of mesenchymal-origin malignant tumors, with multiple histologic variants (5). The malignant fibrous histiocytoma (MFH), a sarcoma subtype, was described for the first time in an international bibliography in 1961. According to Kauffman and Stout (6), MFH is formed by a proliferation of histiocytes with a storiform growth pattern. By 1977, MFH was considered the most common soft tissue sarcoma.

In 2002, the World Health Organization eliminated MFH as an entity with a diagnostic category. Thereafter, this type of neoplasm was included in a group called undifferentiated pleomorphic sarcoma (UPS), also known as nonspecified undifferentiated pleomorphic sarcomas (7,8). This new name was based on a large number of series in the international literature (9-12), which suggested that MFH is the final common route of different tumors that experience a progressive evolution towards cellular dedifferentiation.

The UPS tends to occur in male patients within 50-70 years of age. They are most commonly found in the lower limbs, upper limbs, and retroperitoneum. Based on different published series (13-15), UPS accounts for 2.7-38% of the primary head and neck sarcomas. The normal therapeutic approach for UPS includes surgical treatment; however, radiotherapy (RTD) and/or chemotherapy (CMT) are also applied in some cases.

Given the rarity of UPS, there are few reports that solely include this histological subtype; accordingly, the data regarding the surgical treatment of this malignancy are limited and contradictory.

With this background in mind, the present study was conducted to analyze a series of patients with primary head and neck UPS diagnosis and assess their clinical presentations, therapeutic outcome, follow-up, mortality, overall survival, and disease-free survival (DFS).

Materials and Methods

A retrospective observational analysis was performed on a prospective record database and digital clinical records. Research approval was obtained from the Research Protocols Ethics Committee of our hospital. In addition, the consent of all the patients who participated in the paper was obtained. Patients treated in the head and neck surgical department over the last 11 years (i.e., 2006-2017) were included in the analysis. They had been diagnosed with primary head and neck UPS and had received surgical treatment. The patients with UPS diagnosis receiving a definitive treatment outside our institution were excluded from the study.

Prior to the surgical intervention, all patients were staged in the surgery department through the computed tomography (CT) of the craniofacial mass, neck, and thorax using intravenous contrast. The CT was also used to identify the bone disease; in addition, nuclear magnetic resonance (NMR) imaging was applied to delimit the compromise of the soft tissues. All patients were presented in the multidisciplinary head and neck oncological committee to determine the need for performing further staging studies and the best therapeutic option. The positron emissions tomography/CT (PET/CT) was not routinely used upon diagnosis.

After staging the patients and discussing the cases in the committee, neoadjuvant treatment with RTD and/or CMT was indicated for the tumors deemed unresectable in order to reduce the tumoral mass and make them operable. The most commonly used CMT drug was adriamycin, combined with cisplatin. The neoadjuvant CMT indication was established depending on the tumor size, tumor histological degree, and need for reducing the tumor size before the surgery. The criteria used by our team, based on the oncological committee, to perform adjuvant RTD considered the resections of the positive or marginal margins, tumor size, and high-degree tumors. Marginal resection was defined as a distance of less than 5 mm between the tumor and positive margin where they were in contact with the tumor.

The data collected in the current study included demographic information, tumor characteristics, form of presentation, tumor location, and therapeutic approaches. The tumor

size was determined by CT scan prior to surgical resection or before the initiation of the neoadjuvant treatment. In addition, the postoperative complications were recorded using the Dindo-Clavien classification (16). Postoperative mortality was defined as death caused for any reasons within 30 days of the surgical procedure. The oncological follow-up comprised an outpatient clinical assessment, as well as routine laboratory and imaging assessments (e.g., CT or NMR), performed 1 month after the surgery and every 3 months after that for the first two years, as well as every 6 months after the final follow-up session. The PET/CT was not routinely used in the follow-up. This was performed on a patient-by-patient basis. The assessed survival parameters included overall survival defined as the time from the surgery to the date of death for any reasons or the last follow-up session and DFS defined as the time from the surgery to the date of recurrence or last contact.

Statistical analysis

The quantitative data were expressed as median and range while the categorical variables were presented as absolute and relative frequencies. The DFS and overall survival were calculated using the Kaplan-Meier method. The STATA software (version 13) was used for statistical analysis.

Results

A total of 41 patients diagnosed with primary head and neck sarcoma were treated in our department between January 2006 and October 2017, representing 0.4% of all the patients managed within this period. Out of 41 patient, 11 (36.8%) cases had UPS histological variant, and no patient was excluded (Fig.1). Table 1 presents the demographic data, basal characteristics of the tumor, form of the clinical presentation, and prior treatments of the investigated patients.

Table 1: Demographic characteristics, clinical presentation, and previous treatments of cases with undifferentiated pleomorphic sarcomas

Case n°	Age (years)	Gender	Size (cm)	Histological grade (FNA)	Radiation-induced	T/N/M	Localization	Clinical Presentation	Previous Surgery	Previous RDT or CMT
1	66	M	5.6	High	No	2b/0/0	Skull base/mastoid process	FP	No	No
2	58	M	2.5	Intermediate	Yes	1b/0/0	Maxilla	T	Resection	Yes
3	52	M	6	High	No	2b/0/0	Maxilla	T	No	No
4	60	F	2	High	No	1b/1/0	Tongue	T	No	No
5	56	M	11	High	No	2b/0/0	Supraclavicular fossa	T	No	No
6	65	F	3	Intermediate	Yes	1b/0/0	Parotid gland	T	No	No
7	59	M	3.5	Intermediate	No	1b/0/0	Scalp	T	Resection	No
8	49	F	15	High	No	2b/0/0	Scalp	T	Resection	Yes
9	33	F	1.25	Intermediate	No	1b/0/0	Zygomatic arch	T	No	No
10	13	F	3.5	Intermediate	No	1b/0/0	Orbital fossa	T	Resection	No
11	74	M	2.3	Intermediate	No	1b/0/0	Scalp	T	No	No

TNM: for soft tissue sarcomas and rhabdomyosarcoma: TX: primary tumor cannot be evaluated, T0: there is no evidence of a primary tumor, T1: < 5 cm, T2: > 5 cm. T1-2a: superficial tumor (over the fascia), T1-2b: deep tumor (under the fascia), NX: regional lymph nodes cannot be evaluated, N0: negative regional lymph nodes, N1: positive regional lymph nodes, M0: no metastasis, M1a: lung metastasis, M1b: metastases in another part of the body¹⁷, FP: facial paralysis, T: tumor, RT: radiotherapy, FNA: fine needle aspiration, CT scan: computed tomography scan

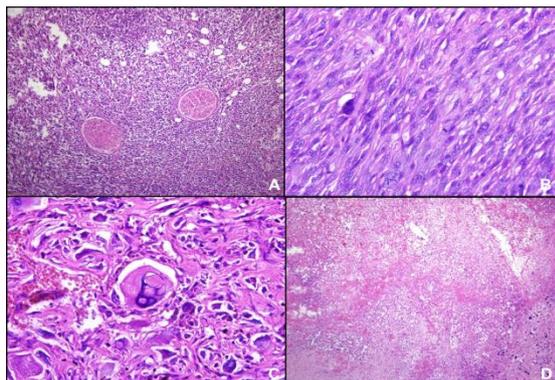


Fig 1: Histologic characteristic of UPS A) Photomicrograph showing tumor cells arranged as a solid tumor with perineural invasion (H and E, x 10). B) Elongated cells with irregular nuclei. Mitosis are also seen (H and E, x 40). C) Bizarre nuclei (H and E, x 40) D) Tumoral necrotic foci (H and E, x 10).

Out of the 11 patients, 5 cases were female, and the median age of the participants was 58 years (age range: 13-74 years). The average tumor size was 5.05 cm (range: 1.25-15 cm), and the scalp was the most commonly affected location (n=3), followed by the upper jawbone (n=2; Fig's 2-3). Four patients had recurrences and were subjected to surgeries in other centers.

Nine patients were operated without neoadjuvant treatment. Two patients, with large tumors, underwent neoadjuvant CMT-RDT due to doubts about the feasibility of resection. One of them had a limited response to neoadjuvant therapy, which led to tumor progression, followed by death without surgical treatment. The remaining one had a good response to treatment, making a surgical approach possible. Table 2 summarizes the type of performed surgery, type of reconstruction, flap used, and state of the margins in the 10 patients undergoing the operation.

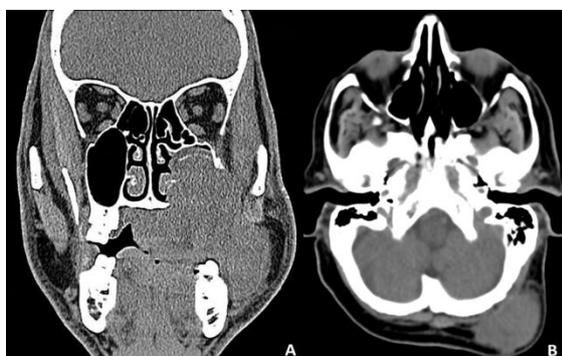


Fig 2: CT of the head and neck showing UPS in different locations. A) UPS located in the left maxilla. B) UPS sited in the scalp.

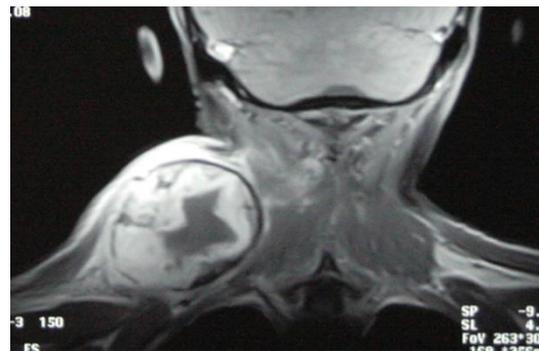


Fig 3: Head and neck MRI showing an UPS located in the right supraclavicular fossa.

All the resections made were ended with free margins (R0 resection; Fig's 4,5). In this regard, 6 out of the 10 resections were marginal. Six patients received RDT as an adjuvant treatment; in addition, two patients received adjuvant CMT-RDT. The postoperative morbidity rate was 10% since a patient developed pulmonary thromboembolism and required intensive care. However, no local complications were recorded in terms of the resection site, flaps, or donor sites. There was also no mortal complication.



Fig 4: UPS situated in the right maxilla compromising the orbital fossa in a male patient that required a maxillectomy with orbital exenteration.



Fig 5: UPS situated in the right maxilla compromising the orbital fossa in a 58-year-old male patient. A maxillectomy with orbital exenteration was performed. A) The picture shows the harvesting of the latissimus dorsi myocutaneous flap. B) Final results of reconstructive procedure.

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The mean follow-up duration was 52 months in the patients undergoing the operation. Three and two patients had a relapse at local and distance levels, respectively, and the remaining ones had local and regional relapses. The 1-, 3-, and 5-year DFS rates were 70%, 50%, and

50%, respectively; in this regard, the average DFS was obtained at 36 months. In addition, the 1-, 3-, and 5-year overall survival rates were estimated at 100%, 100%, and 83%, respectively (Table.2). Only one patient died after developing a distant disease.

Table 2: Analysis of patients with undifferentiated pleomorphic sarcoma that were surgically treated in terms of recurrence, disease-free survival, mortality, and follow-up.

Case No.	Surgery	Type of surgery	Reconstruction	Type of flap	Margins	Recurrence	DFS (months)	Status	Follow-up (months)
1	Yes	Temporalectomy	Pediculated flap	Temporal flap	Marginal	Yes	8	Alive	10
2	Yes	Maxilectomy	Free flap	ALT	Marginal	Yes	21	Dead	40
3	-	-	-	-	-	-	-	-	-
4	Yes	En bloc resection	Rotation flap	None	Marginal	Yes	4	Alive	8
5	Yes	En bloc resection	Pediculated flap	PMMF	Marginal	No	79	Alive	79
6	Yes	Parotidectomy	Primary closure	None	Marginal	No	45	Alive	45
7	Yes	En bloc resection	Free flap	ALT	Negative	No	89	Alive	89
8	Yes	En bloc resection	Free flap	LDMF	Negative	Yes	3	Alive	20
9	Yes	En bloc resection	Rotation flap	None	Negative	No	115	Alive	115
10	Yes	En bloc resection	Free flap	ALT	Marginal	Yes	98	Alive	122
11	Yes	En bloc resection	Primary closure	None	Marginal	Yes	36	Alive	37

ALT: anterolateral thigh flap, PMMF: pectoralis major myocutaneous flap, LDMF: latissimus dorsi myocutaneous flap, DFS: disease-free survival
Case 3 was unresectable and subjected to primary chemotherapy-radiotherapy

Discussion

There are numerous case series about sarcomas (but not exclusively UPS) in the current literature. Large case series investigating the neck and head sarcomas series constitute the grounds for discussion in this area. The MFH (i.e., UPS subtype) was the most common subtype in these series. The UPS tends to occur in male patients within the age range of 50-70. They are most commonly found in the lower limbs, upper limbs, and retroperitoneum. The incidence rate of UPS in our series was obtained at 26.8%. In a case series conducted on 17 cases with the neck and

head MFH by Hardison et al.(18), the most commonly affected location was the scalp, and 66% of these tumors were classified as having a high histological degree. In our series, three tumors were located on the scalp, representing the most common location, followed by the upper jaw (n=2). Unlike in the study by Hardison et al. (18), in the current study, the predominant histological degree was intermediate (n=6).

Similar to our study, Barosa investigating 29 cases of primary neck and head soft tissue sarcomas reported that the most common manifestation form of this type of tumor was a

tumoral mass growing in just a few weeks or months (13,14,19). In the current study, 10 of the 11 tumoral masses were located in different locations, and just one was located at the base of the cranium manifesting as facial paralysis. In the series reported by Barosa (19), the osteosarcoma was the most common tumor.

For staging the UPS, as for the rest of the sarcomas, the CT of the craniofacial mass, neck, and thorax with intravenous contrast is applied. The NMR is used to determine the compromise of the soft tissues. The studies about the use of PET/CT in sarcomas have shown that the standardized uptake values proportionally correlate with the histological degree, aggressiveness, and mortality (20). The PET/CT is a method with high sensitivity; however, this modality is not specific for the diagnosis of sarcomas. Several investigations have attempted to define the role of this approach (20-22); however, the use of this modality remains controversial (23-25). Since the investigation of our series began 11 years ago, routine PET was not used in all cases. In a study investigating the reconstructive outcomes in patients with neck and head sarcoma, among whom MFH was the second most common sarcoma subtype after spinocellular tumors (26), the anterolateral thigh flap (ATF) was the most commonly used flap. In our series, 2 out of 11 patients were reconstructed with anterolateral thigh flaps.

The therapeutic pillars of the sarcoma include surgical treatment, RDT and/or CMT. The RDT has been clearly shown to be capable of reducing the incidence of local recurrence; accordingly, it is considered a key part of UPS treatment (27,28). According to the literature, RDT in the head and neck sarcomas is indicated if facing histological high-degree tumors, positive surgical margins, lesions over 5 cm, and/or recurrent lesions (29). In our institution, the same criteria exist for the use of adjuvant RDT; however, these patients are always discussed in the oncological committee. The most serious complication is the appearance of radio-induced sarcomas (less than 5%) (30-32), which appeared in 2 cases in our series.

According to the series published by Peng et al. (13), the use of neoadjuvant or adjuvant CMT continues to be debated. In a meta-analysis (33), it was reported that the addition of

CMT improved the global survival in less than 10% of the cases. Studies with more limited evidence have shown an increase in IFS with ifosfamide and doxorubicin (34,35). Finally, Peng et al. (13) stated that CMT is a strategy used in high-degree sarcomas and would reduce the risk of recurrence in soft tissue type localized sarcomas (36). Tran et al. (37) proposed that unresectable sarcomas, sarcomas extending to unusual anatomical sites (e.g., the base of the cranium), and/or aggressive sarcomas could benefit from chemotherapy treatment. The CMT drugs used by our service include adriamycin plus ifosfamide or platin plus adriamycin, which were decided upon in the tumor committee. Among the prognostic factors, the age of > 60 years, tumor size of > 5 cm, deep locations, and high histological degree have been described as unfavorable. The status of the margins and tumor histologic degree are associated with the recurrence-free survival, while the histologic degree and age affect the global survival (2,3).

The rate of the local recurrence of all soft tissue sarcomas varies from 20% to 30% (38). This rate is higher among the patients with the neck and head sarcomas. Local recurrence is associated with close or positive margins, high-grade tumors, and tumor size of > 5 cm. In our series, the one- and two-year local recurrence rates were 11.5% and 22.7%, respectively. This rate was associated with oral cavity and mandible involvement, close or positive margins, and radio-induced sarcomas. Most of the recurrences occur in the first two years of follow-up, similar to our series where the DFS by one year is 70%, falling to 50% for years 3 and 5.

In our series, the presence of multiple cases of positive or close margin after surgical removal was due to the tumor size and its difficult localization within the head and neck. Our follow-up included clinical examination and image study (e.g., CT or NMR). Most of the recurrences located at a local level can be resolved with surgical treatment, thereby prolonging the survival (39,40).

The 5-year DFS rate in our series was 50%. This rate oscillates between 34% and 70% in the published series (38,41,42). In the analysis of the SEER database (13), the 5-survival rate was estimated at 60%. This is possibly due to the difficulty of achieving free margins given

the proximity of the region's anatomical structures.

This retrospective case series has some limitations related to the study design. The present study solely investigated UPS; however, most of the published series included different tumor types in various locations. Head and neck sarcomas represent a heterogeneous group of tumors with different prognostic characteristics. The identification of the behavior of these tumors, their response to treatment, follow-up, and morbimortality is important to assess their prognoses.

Conclusion

Primary head and neck sarcomas are uncommon. The UPS is the most common tumor type, tending to be intermediate and high-grade tumors. Despite the new treatment modalities, surgery continues to be the gold standard of this malignancy. Surgical resection is feasible in more than 90% of patients, reaching an acceptable overall survival and DFS.

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