AUS DEM LEHRSTUHL FÜR MUND-KIEFER-UND GESICHTSCHIRURGIE
DIREKTOR: PROF. DR. DR. TORSTEN E. REICHERT
DER FAKULTÄT FÜR MEDIZIN
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PRIMARY AND SECONDARY LEIOMYOSARCOMA OF THE ORAL AND PERIORAL REGION- CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSIS OF A RARE ENTITY WITH A REVIEW OF THE LITERATURE

Inaugural-Dissertation
zur Erlangung des Doktorgrades
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Primary and Secondary Leiomyosarcoma of the Oral and Perioral Region—Clinicopathological and Immunohistochemical Analysis of a Rare Entity With a Review of the Literature

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Purpose: Leiomyosarcoma (LMS) rarely occurs in the head and neck region. These tumors present with a wide range of clinical features, so the diagnosis is predicated on conventional microscopic findings coupled with immunohistochemical analysis.

Patients and Methods: Clinical and histologic data of 7 patients with LMS of the head and neck were recorded retrospectively. In addition to routine immunohistochemistry, staining for cell cycle regulator proteins p16 and p21 was performed.

Results: Five LMSs (4 intraoral, 1 dermal cheek) occurred primarily in the oral and perioral region. Two LMSs (parietal and sinonasal) were diagnosed as metastases originating from the uterus and pelvis. Treatment of the primary LMSs consisted of radical tumor resection with clear margins. Distant metastases from LMSs were irradiated or excised as palliative treatment. Three of 5 patients (60%) with primarily excised LMS developed recurrence after an average of 7 months, with lung metastases occurring after 17 months. In 1 patient, cervical lymph node metastases were detected after 10 months. Of all patients, 5 died after an average survival period of 2.4 years. The mean survival period of the 5 patients with primary LMS of the head and neck was 3.3 years. All tumors were positive for vimentin and α-smooth muscle actin, with 57% of tumors showing positive nuclear expression of p16 and 71% of p21. Lack of p16 nuclear expression was associated with a shorter mean survival time (1.3 vs 4.3 yr for p16 positivity).

Conclusion: Lung and cervical lymph node metastases often occur in LMS of the head and neck. Presurgical staging, including gynecologic examination, whole-body computed tomography, and sometimes positron-emission or computed tomography, to rule out LMS metastasis is mandatory. Surgical resection of the tumor should be given top priority. Lack of p16 reactivity may have a prognostic value for LMS because it was related to a trend toward poorer survival.

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Leiomyosarcomas (LMSs) are rare tumors that arise from smooth muscle cells of the myometrium, gastrointestinal tract, or retroperitoneum.[1] They account for 7% of soft tissue sarcomas.[2] LMSs are found predominantly in the uterus, gastrointestinal tract, or retroperitoneal space,[3] whereas LMSs in the head and neck region account for only 3%, most likely because of the paucity of smooth muscle tissue.[4-6] Fewer than 0.1% develop in the oral cavity.[7] LMSs of the oral and perioral region are divided further into 3 main subgroups: LMS of the oral soft tissue, LMS of the facial skin, and LMS of the jawbone. Separate from these are primary LMSs of the head and neck and metastases originating from the female genitalia, predominantly the uterus.[8] LMSs of the head and neck are rare tumors with various clinical and histopathologic appearances. Origins of the LMS of the head and neck are probably in the arterial tunica media, ductus lingualis, circumvallata papillae, and pluripotent mesenchymal cells.[6] The most frequent sites are the sinonasal tract (19%), the skin and soft tissue (16%), and the esophagus (12%).[6]

The prognostic significance of the localization of LMS in the head and neck region is unclear. Because of the rare occurrence and poor prognosis of LMS, existing systematic data are insufficient and evidence of effective therapy is scarce. The new World Health Organization classification indicates a poor prognosis for primary LMS of the sinonasal tract and a variable outcome of primary LMS of the larynx.[1] The prognosis of LMS in the oral and maxillofacial region is also poor, with a large percentage of recurrence and metastasis.[1,5] The estimated 5-year disease-specific survival rate (DSS) for primary oral LMS is 55%.[1,2] The respective 5-year DSS data of primary LMS of the oral and perioral soft and hard tissues indicate a survival rate from 32% to 62%[2,7,9] (Table 1),[2,4,7,9-13] because LMS of the oral soft tissue has a better prognosis than LMS infiltrating the jaws, which has a significantly higher recurrence rate.[1,2] The reason for this difference may be easier follow-up treatment of the soft tissue region, with the possibility of earlier detection of an initial tumor recurrence than that of the jawbone, which can be followed only by imaging methods.

Diagnosis of these tumors is often challenging. Immunohistochemistry for vimentin, desmin, or α-smooth muscle actin (ASMA) provides features of smooth muscle cell differentiation, which is critical for the diagnosis of LMS.[14]

Proto-oncogenes and suppressor oncogenes that have contrary functions in cellular growth normally regulate cellular proliferation. Apart from multiple other changes, neoplastic development is characterized by a loss of cell cycle control. Proteins p16 and p21 are cell cycle regulators that have been studied in different human neoplasms, including uterine smooth muscle tumors.[15,16]

By inactivating the cyclin-dependent kinase (CDK) that phosphorylates the retinoblastoma protein, protein p16 acts as a CDK inhibitor that slows down the progression of the cell cycle. Protein p21 is also a potent CDK inhibitor and binds to and inhibits the activity of cyclin-CDK2 or -CDK1 complexes and thus functions as a regulator of cell cycle progression at the G1 phase.

The cell cycle regulators p16 and p21 are tightly controlled by tumor suppressor protein p53,[17] which is often mutated and overexpressed in LMS.[18,19] The latter findings suggest a connection between tumor progression and immunohistochemical expression levels of p16 and p21. The overexpression of p16 appears to distinguish malignant LMSs from benign leiomyomas.[20] The aims of this retrospective study were to document the clinical presentation, clinical course, and treatment of the rare entity of primary LMS of the oral cavity and to analyze the impact of cell cycle proteins p16 and p21 as an adjunct to conventional immunohistochemical criteria of LMS of the head and neck region.

Patients and Methods

Clinical treatment, follow-up, and histologic data of 7 patients with primary LMS of the head and neck were recorded after therapy. The out- and inpatient medical records of the university clinics of oral and maxillofacial surgery in Regensburg and Lübeck, Germany from 1996 through 2008 were reviewed. Clinical data were correlated with tumor grade, which was assessed using the National Cancer Institute system.[21] Owing to the retrospective nature of the study, it was granted a written exemption of the institutional review board standards of individual institutions by the universities of Regensburg and Lübeck. In addition, all patients signed an informed written consent agreement allowing the use of follow-up data and histologic specimens for research purposes.

The diagnosis of a distant metastasis of an occult primary tumor was excluded in 5 cases of primary LMS of the head and neck region by a full gynecologic examination and whole-body computed tomography (CT) or magnetic resonance imaging (MRI) at the time of initial diagnosis. An additional positron-emission tomographic or CT scan was performed in the primary LMS cases when the CT or MRI findings were unclear as to the differential diagnosis of a distant metastasis from other origins.

IMMUNOHISTOCHEMISTRY

Formaldehyde-fixated paraffin-embedded tissue blocks from every patient were stained with

Table 1. LITERATURE SURVEY OF EPIDEMIOLOGY, TREATMENT, AND CLINICAL COURSE OF PRIMARY LEIOMYOSARCOMA OF THE HEAD AND NECK REGION

Source	Patients (n)	M:F	Age (yr)	Primary Localization (n)	Therapy (n)	Relapse (%)	Distant Metastasis (%)	Follow-Up After Treatment
Mietttinen et al[11] (1984)	6 (5 case reports + 1 own case)	5:1	18-62	mandible (6)	OP (6), RT (1), CT (2)	67	50	50% after 24-60 mo,† 33% −T after 24 mo,* 1 patient −T after 24 mo*
Carter et al[12] (1999)	11	1.2:1	40	jaw bone (11)	OP (10), RT (3), CT (2)	NES	36	36% after 36 mo,† 36% −T after 12 mo,* 18 +T after 24 mo*
Dry et al[10] (2000)	10	1:1.5	34	jaw bone (5), oral soft tissue (5)	OP (9), RT (1), CT (2), unknown (1)	20	33	50% after 20 mo,† 40% −T after 49 mo*
Ethunandan et al[2] (2007)	64	1.3:1	43	jaw bone (38), oral soft tissue (20), facial skin (6)	OP (60), RT (14), CT (11)	34	35	5-yr DSS 55% total, 43% with bone infiltration, 19% with metastasis
Izumi et al[9] (1995)	60	1.4:1	42	jaw bone (27), maxillary sinus (14), oral soft tissue (18), fascial skin (1)	OP (55), RT (4), CT (39), unknown (2)	44	35	2-yr DSS 66%, 5-yr DSS 32% total
Kratochvil et al[13] (1982)	20	4:1	65-70	jaw bone (8), skeleton bones (12)	OP (18), RT (6), CT (2)	NES	37	35% after 24 mo,† 45% after 21 mo,* 20% NES
Montgomery et al[4] (2002)	13	1.2:1	47	jaw bone (5), oral soft tissue (3) fascial skin (2), neck muscles (2), pharynx (1)	OP (9), unknown (4)	27	55	23% after 67 mo,† 38% −T after 50 mo,* 8% +T after 24 mo,* 31% NES
Vilos et al[7] (2005)	50	1:1.3	44	jaw bone (34), oral soft tissue (15), maxillary sinus (1)	OP (46), RT (14), CT (13), unknown (4)	NES	32	5-yr DSS 62%
Present study	7	1:1.3	60	oral soft tissue (4), fascial skin (1), distant metastasis (2)	OP (6), RT (2)	43	71	71% after 29 mo,† 29% −T after 67 mo*

Abbreviations: CT, chemotherapy; DSS, disease-specific survival rate in years; F, female; M, male; NES, not elsewhere specified; OP, operation with radical resection; RT, radiation therapy; +T, with tumor; −T, without tumor.

* Alive.

† Died.

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hematoxylin and eosin. For immunohistochemical markers vimentin, desmin, ASMA, and Ki-67, results of routine immunohistochemistry were obtained. Staining for cell cycle regulator proteins p16 and p21 also was performed with commercially available antibodies against p16 (Mtm Laboratories, Germany) and p21 (ScyTek, Zytomed Systems, Berlin, Germany). The sources and dilutions of all primary antibodies are presented in Table 2. For the negative control, representative sections were incubated with normal rabbit serum (1:100; DAKO, Glostrup, Denmark) and processed simultaneously as described earlier. Only nuclear staining was considered a positive reaction for p16 and p21. The evaluation of immunohistochemical staining was performed semiquantitatively and qualitatively by analyzing the percentage of positively stained tumor cells in 5 representative high-power fields, as explained later.[22]

Briefly, the percentage of tumor cells with positive staining was estimated by counting 1,000 tumor cells. The number of positively stained tumor cells was scored on a scale of 0 to 4 (0, no tumor cells; 1, 10% tumor cells; 2, 10% to 25% tumor cells; 3, 26% to 50% tumor cells; 4, 50% tumor cells). Nuclear staining intensity was evaluated according to the intensity of positive immunostaining as negative (−), weak (+), moderate (++), or strong (+++).

Detection of the bound antibody was performed with the ChemMate detection system (Dako ChemMate detection system, Hamburg, Germany) (alkaline phosphatase) and an immunostaining automatic machine (Dako Autostainer, Hamburg, Germany) according to the manufacturers' protocols (Table 2).

Results

CLINICAL AND FOLLOW-UP DATA

Seven patients (3 male and 4 female) with primary LMS of the head and neck region were evaluated. The average age was 60 years (25 to 93 yr). Five LMS tumors (4 intraoral, 1 in dermal cheek) occurred primarily in the oral and perioral region (Table 3, Fig 1A-D). Two LMS tumors (parietal and sinonasal) were diagnosed as distant metastases originating from the uterus and pelvis. In these 2 cases, therapy of the primary LMS consisted of surgical tumor resection with clear margins. In 3 cases, a selective neck dissection was performed, and 1 patient underwent irradiation after surgery. Distant LMS metastases were treated with palliative radiation or excised (Table 3). Independent of the selected therapy, 3 of 5 patients (60%) with primary LMS developed local recurrence after an average of 7 months (3 to 10 mo); in addition, lung metastases occurred after 17 months in all patients. In 1 patient, cervical lymph node metastases were detected 10 months after solitary tumor resection.

Distant metastases in the head and neck region of the LMS of the uterus and pelvis developed parietally and ethmoidally and in the cavernous sinus and retroauricularly and in the median skullcap, respectively. Furthermore, metastases occurred in the lung and submandibular gland (Table 3).

Five patients with metastases died after an average survival time of 2.4 years (1.0 to 5.3 yr). Two patients with primary LMS of the dermal cheek and the floor of the mouth were still alive after the end of the maximum 6.5-year follow-up period of this study without metastases or recurrence (4.7 and 6.5 yr, respectively; Table 3).

The mean survival period of all patients was 3.3 years (1.0 to 6.5 yr). Because of the small sample, the average survival period of the 5 patients with primary LMS of the head and neck was the same at 3.3 years (1.0 to 6.5 yr).

HISTOLOGY

All LMS cases in this research series were assessed for tumor depth, presence of circumscribed versus infiltrative tumor borders, mitotic counts per 10 high-power fields (5 sets counted), necrosis, nuclear pleomorphism, vascular invasion, and the occurrence and environment of inflammatory components. Routine hematoxylin and eosin–stained LMS

Table 2. PRIMARY ANTIBODIES USED IN THIS STUDY

Antibody	Clone	Producer	Dilution	Pretreatment
p16	E6H4	Mtm Laboratories	—	Peroxidase blocking system, pH 9
p21	DSC-60.2	Zytomed Systems	1:50	Target Retrieval Solution 1:10, pH 6.1
Vimentin	V9	Dako	1:4,500	Target Retrieval Solution 1:10, pH 9
Desmin	D33	Dako	1:200	Target Retrieval Solution 1:10, pH 9
ASMA	1A4.(1)	Dako	1:300	Target Retrieval Solution 1:10, pH 9
Ki-67	MIB1	Dako	1:1,000	Target Retrieval Solution 1:10, pH 6.1

Abbreviation: ASMA, α-smooth muscle actin.

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Table 3. CLINICAL DATA OF THE STUDY PATIENTS

PN	Age (yr)/Gender	Localization in Head and Neck Region	T (cm)	Bone Infiltration (Histologic)	Initial Treatment in Head and Neck Region	Relapse or Metastasis After Treatment (mo)	Follow-Up (yr)
1	75/M	lower lip	0.8	no	tumor resection with clear margins	cervical (3 mo); submandibular, supraclavicular LN, lung (10 mo)	1.6†
2	74/F	cheek skin	2.5	no	tumor resection with clear margins	no	4.7*
3	39/F	trigonum retromolare	1.5	yes	tumor resection with clear margins + cervical LN dissection + radiation therapy (49.6 Gy)	masticatory muscles (10 mo); lung, liver, kidney, bone, adrenal gland, stomach, thyroid gland (11 mo)	1.0†
4	73/M	hard/soft palate	2	no	tumor resection with clear margins + cervical LN dissection	pharynx, palate, right masticatory muscles (7 mo), lung (28 mo)	2.7†
5	25/M	floor of mouth	2.5	no	tumor resection with clear margins + cervical LN dissection	no	6.5*
6	93/F	skullcap (metastasis of pelvic LMS)	4	yes	tumor resection with clear margins	submandibular gland, lung (14 mo)	5.3†
7	44/F	sinonasal tract (metastasis of uterine LMS)	NES	yes	palliative radiation therapy (56 Gy)	lung (simultaneous)	1.4†

Abbreviations: F, female; LMS, leiomyosarcoma; LN, lymph node; M, male; NES, not elsewhere specified; PN, patient number; T, tumor size at primary diagnosis.

* Alive.

† Died.

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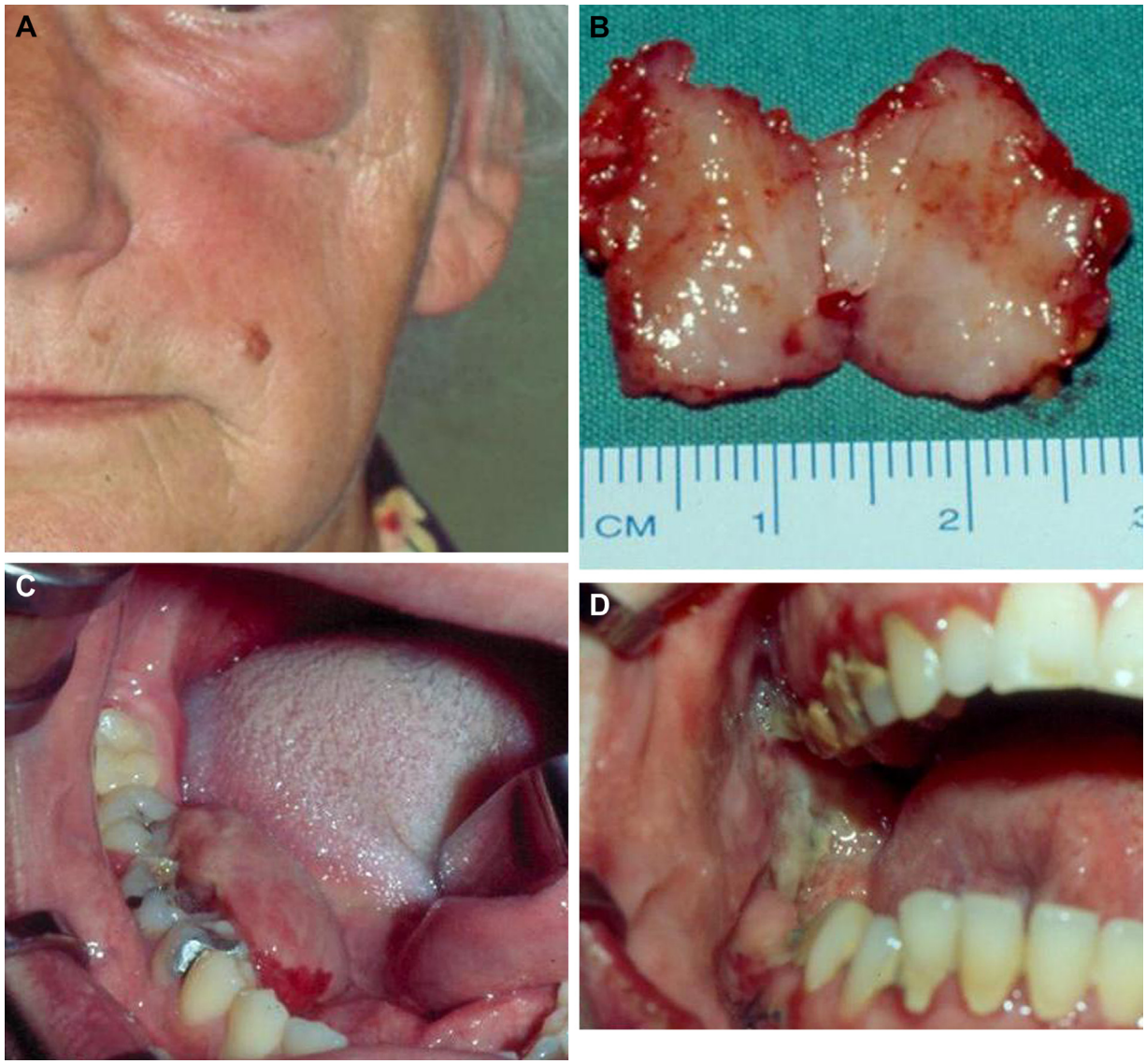

FIGURE 1. *A,* En face view of a leiomyosarcoma of the left cheek. *B,* Radically resected leiomyosarcoma of the left cheek. *C,* Leiomyosarcoma at the right side of the floor of the mouth (intraoral tumor mass with necrotic ulcer measuring roughly 3.0 × 3.0 cm). *D,* Intraoral view of a leiomyosarcoma in the right retromolar triangle.

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slides displayed a rough, tubercular, and infiltrating process of growth with fusiform or polygonal cells (Fig 2A). Both cell forms could be seen regularly. A cytoplasm seam with a fine fibrillary eosinophilic texture was always traceable, often with physiologic mitotic figures. At higher magnification, the tumors exhibited perpendicularly arranged fascicles of sharply marginated groups of spindle cells with eosinophilic cytoplasm and characteristic cigar-shaped nuclei, hyperchromatic blunt-ended nuclei, and scattered paranuclear vacuoles, which constitute the typical focal histologic features of LMS. Mitotic activity was found in all tumors (4 to 40 mitoses per 10 high-power fields), and necrosis was present in all cases. Vascular invasion was only minimally visible (Fig 2A, B). All lesions had minimal inflammation that, when present, consisted of scattered lymphocytes or lymphoid aggregates. The amount of collagen fibers between tumor cells was low. According to the National Cancer Institute grading system,[21] 2 of the 5 primary LMSs of the head and neck region were assigned to grade 1, 2 to grade 2, and 1 to grade 3.

Immunohistochemically, all tumors were positive for vimentin (5 of 5) and ASMA (5 of 5). Two of 3 examined tumors expressed desmin. In 2 tumors, the proliferation marker Ki-67 showed positive immunoreactivity. High magnification disclosed blunt-ended nuclei and delicate cytoplasmic fibrils, with cells displaying striking nuclear pleomorphism (Figs 2B, 3A, B). The

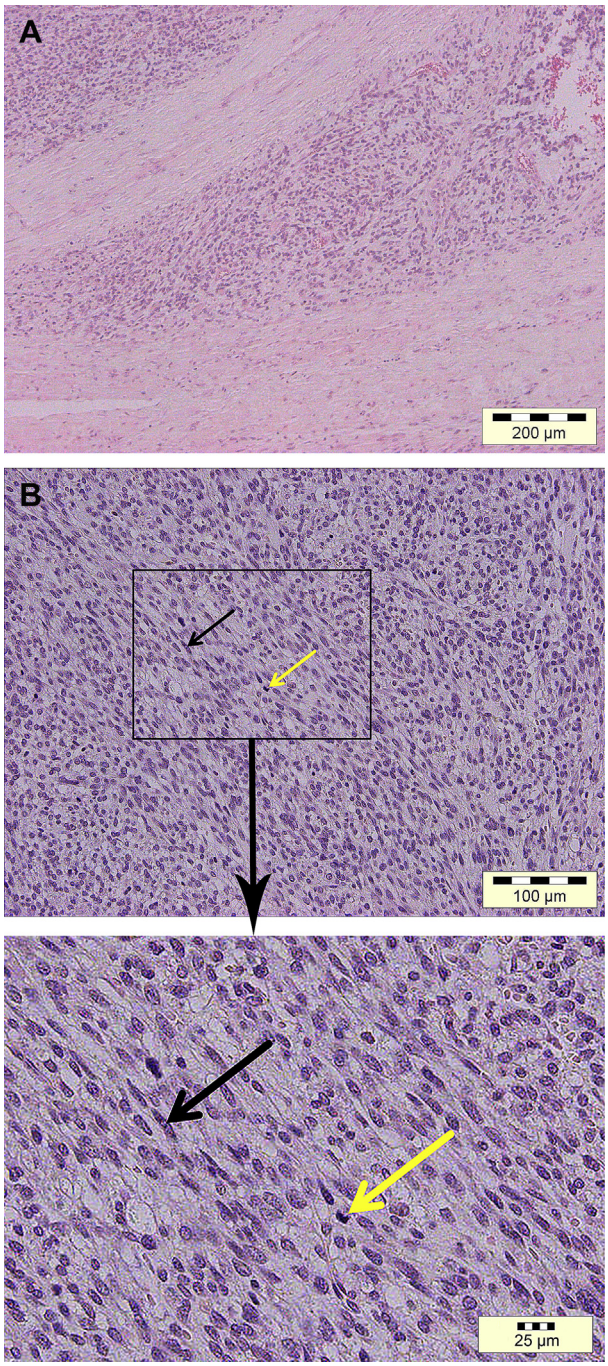

FIGURE 2. *A,* Hematoxylin-and-eosin survey view shows a leiomyosarcoma with a rough trabecular process of growth. *B,* Hematoxylin-and-eosin detail view displays microscopic analysis, which shows intersecting, sharply marginated groups of spindle cells with eosinophilic cytoplasm, striking nuclear pleomorphism, and characteristic cigar-shaped nuclei (*black arrow*). Highly magnified detail view shows moderately increased scattered mitotic activity (*yellow arrow*), characteristic cigar-shaped nuclei (*black arrow*), and delicate cytoplasmic fibrils.

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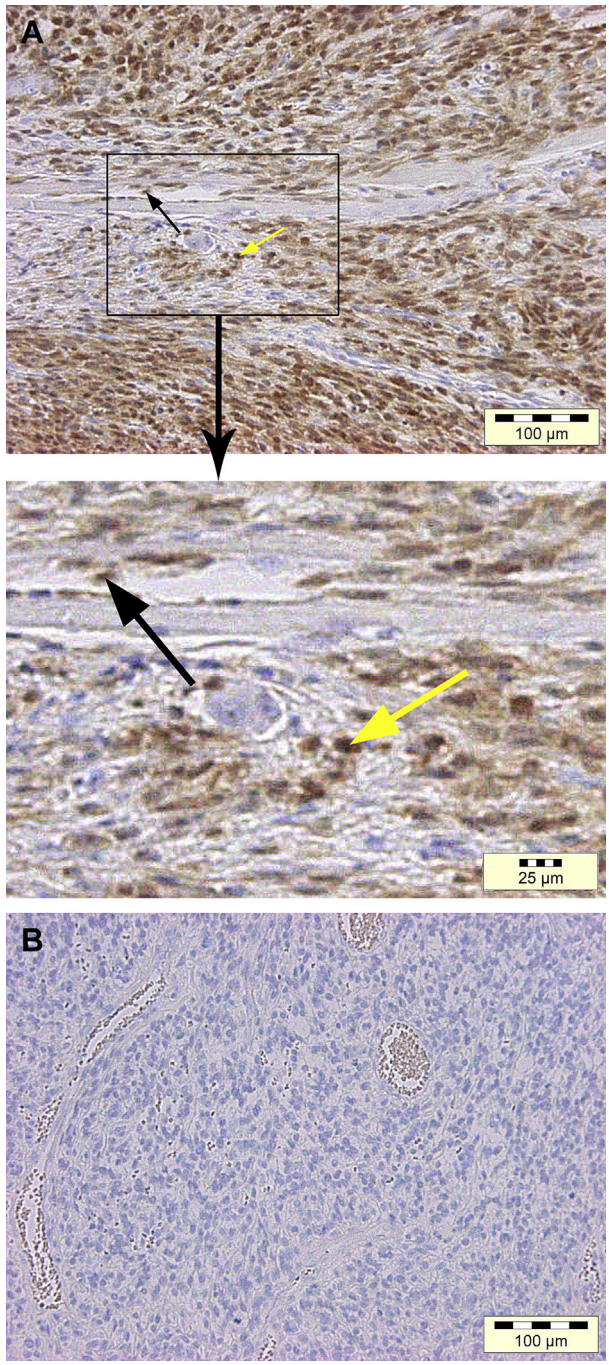

FIGURE 3. Immunohistochemical analysis for expression of proteins p16 and p21 in primary leiomyosarcoma of the head and neck. *A,* Diffuse nuclear p16 expression in a leiomyosarcoma (*brown area*). Magnified detail view shows diffuse nuclear p16 positivity (*black and yellow arrows*). *B,* No p21 expression.

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proliferation rate of the primary LMS of the lip was 50%, whereas that of the distant metastasis of the LMS of the uterus was only 5%. Four of 7 tumors (57%) showed positive immunoreactivity for p16 (Fig 3A), whereas protein p21 expression was significantly increased in only 2 cases. The overall expression of all immunohistochemical markers according to the LMS location is presented in Table 4.

Table 4. ANALYSIS OF IMMUNOHISTOCHEMICAL STAINING

PN	Primary Localization	Vimentin	Desmin	ASMA	Ki-67	p16	p21	Follow-Up (yr)
1	lower lip	100% Pos	Neg	10% Pos	50%	Neg	2% Pos	1.6†
2	skin of cheek	Pos	Neg	Pos	NES	2%	5%	4.7*
3	retromolar triangle	Pos	Pos	Pos	NES	Neg	25%	1.0†
4	palate	NES	NES	NES	NES	100% Pos	Neg	2.7†
5	floor of mouth	Pos	Neg	Pos	NES	5%	5%	6.5*
6	pelvis	NES	NES	NES	NES	80%	25%	5.3†
7	uterus	100% Pos	2% Pos	100% Pos	5%	Neg	Neg	1.4†

Abbreviations: ASMA, α-smooth muscle actin; Neg, negative staining; NES, not elsewhere specified; PN, patient number; Pos, positive staining.

* Alive.

† Died.

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The average survival period for these patients was 4.3 years (2.7 to 6.5 yr). Lack of p16 was associated with a shorter average survival period (1.3 vs 4.3 yr for p16 positivity; Table 4). The 2 patients without recurrence and metastases showed an expression of p16 (Fig 3A). Five of 7 tumors (71%) were positive for protein p21. The mean survival period of these p21-positive patients was 3.8 years (1.0 to 6.5 yr), whereas the survival period of p21-negative patients was 2.1 years (1.4 to 2.7 yr; Fig 3B). As already mentioned, the small sample did not allow a statistical calculation of any correlation. Therefore, the expression of the 2 proteins was not significantly associated with survival. There was no correlation between protein expression and localization of the tumor. The analyzed immunohistochemical markers p16 and p21 could not be used to distinguish primary LMSs from distant metastases originating in the uterus and pelvis.

Discussion

This study analyzed the impact of protein expression of cell cycle regulators p16 and p21 in primary and metastatic LMSs of the head and neck region. Because the latter site is a very uncommon location for LMS, only a few cases were available for detailed analyses in this series. Therefore, a statistical correlation of prognosis and tumor localization was not possible. However, this is the first study that has examined a small series of primary and metastatic head and neck LMSs for the expression of proteins p16 and p21. The 5 patients with a primary LMS showed an average survival period of 3.3 years (1.0 to 6.5 yr). Of these, 2 patients survived 4.7 and 6.5 years, respectively (5-yr DSS, 40%). After an average of 17 months, 3 of 5 cases (60%) showed lung metastases. The current literature describes a probability of developing distant metastases of only 35% in primary oral LMS[1,2] (Table 1). The lung and liver are predilection sites for distant metastases of LMS of the head and neck.[1,6]

In addition to the more frequent distant metastases of primary LMS of the head and neck region, in 15% of cases, metastases can spread to the regional lymph nodes.[2,6,10] In the present study, 1 patient with primary LMS of the lip developed metastases in the regional lymph nodes. The local recurrence rate is approximately 35%[2] (Table 1), which is comparable to the frequency of recurrence in the present study (43%).

In addition to primary LMS of the head and neck, secondary lesions can present as distant metastases from tumors that originate in the female genitalia, especially the uterus (Table 5).[8,23-30] There is obviously a hematogenous spread from the uterus by the lung to the oral cavity. Hence, these metastases mainly occur at highly vascularized areas, such as the masseter muscle or the tongue. To differentiate primary LMS from distant metastasis, a thorough preoperative gynecologic examination combined with whole-body CT or MRI, as performed in the present cases, is recommended. For further differential diagnosis, additional positron-emission tomography or CT is reserved for unclear primary LMSs of the head and neck that show atypical findings on whole-body CT or MRI scan.

Treatment of primary LMS consists of radical tumor resection with the goal of histologically clear margins. This is crucial to determine the true course of the disease and the long-term prognosis.[31-33]

Chemotherapy is generally reserved for palliative cases, such as inoperable primary tumors or metastatic spread.[2,4,10,32] Primary LMSs and distant metastases are ordinarily resistant to radiation treatment.[2,4,5,10] Hence, no remission was detected in the present study.

Immunohistochemically, LMSs are usually positive for desmin, vimentin, and ASMA. These markers are essential for the diagnosis of LMS. Apart from vimentin and ASMA, the importance and constant overexpression of desmin could not be confirmed by the present

Table 5. LITERATURE SURVEY OF CLINICAL COURSE OF LEIOMYOSARCOMA WITH DISTANT METASTASIS IN THE HEAD AND NECK REGION

Source	Age (yr)	Gender	Primary Localization	Localization of Metastasis	Treatment	Follow-Up (yr)
Allen et al[23] (1993)	66	M	leg	hard palate	OP + RT + CT	2†
Allen et al[23] (1993)	61	M	upper leg	mandible	OP + RT + CT	3*
Allen et al[23] (1993)	65	F	uterus	lower lip	OP + CT	1.4*
Aslan et al[24] (2008)	76	F	uterus	temporal muscle	OP − RT	3*
Bogart et al[25] (1990)	58	F	lung	palate	CT + RT	0.4†
Kaziro et al[26] (1981)	59	F	uterus	tongue	none	unknown
Nusrath et al[27] (2006)	65	F	uterus	masseter muscle	OP + CT	2.3†
Sandruck et al[28] (2004)	39	F	uterus	sphenoid	OP + CT + RT	1.1†
Uchino et al[29] (1996)	54	F	uterus	skull	OP + CT	2†
Kim et al[8] (2009)	56	F	uterus	right maxilla	none	0.3†
Vora and Levin[30] (2003)	62	F	uterus	tongue	none	NES†
Present study	44	F	uterus	sinonasal tract	OP + RT	1.4†
Present study	93	F	pelvis	skullcap	OP + RT	5.3†

Abbreviations: CT, chemotherapy; F, female; M, male; NES, not elsewhere specified; OP, operation; RT, radiation therapy.
* Alive.
† Died.

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immunohistochemical data compared with a study by Montgomery et al[4] that found an expression of desmin in 10 of 12 cases. Although desmin was positive in only 40% of cases in this study, the Ki-67 proliferation rate was analyzed in 2 cases and showed positive nuclear staining of 5% and 50%, which is in line with the results of other studies of head and neck LMSs.[4] Other investigators have reported a Ki-67 proliferation rate of 15%.[34]

Tumor-suppressor protein p16 regulates the cell cycle in the G1 phase by inhibiting the cell proliferation through the inhibition of cyclin D-dependent kinase complex 4/6.[35] A decreased p16 expression has been detected in 5% to 33% of LMSs.[36,37] A lack of nuclear p16 expression in neoplastic cells seems to be associated with progressive tumor size and decreased overall survival.[38] However, there are only limited data regarding the function and impact of cell cycle regulator proteins p16 and p21 in mesenchymal neoplasms. Also, the data on p16 and p21 expressions in larger studies of uterine smooth muscle tumors are incomplete,[39-41] so that there are no comparable results. In the present study, 4 of 7 cases showed an increased nuclear expression (>25%) of p16. Although the p16-negative cases had an average survival period of 1.3 years, the p16-positive cases survived 4.3 years on average. Although this difference is not statistically significant because of the small number of cases, it indicates a worse prognosis when there is a lack of p16 activity.

Protein p21 is a cyclin kinase inhibitor that is regulated by the tumor suppressor p53. Protein p21 leads to cell cycle arrest and plays a crucial role in repairing DNA damage.[42,43] Commonly, LMSs express p21, whereas lack of p21 seems to be associated with an increased risk of recurrence.[44] In the present study, the mean DSS in the p21-negative cases (2.1 yr) was decreased compared with the p21-positive cases (3.8 yr). As in the case of p16, a statement regarding the impact of p21 expression on DSS and the chance of recurrence based on a statistical calculation could not be made.

Neither p16 nor p21 reactivity could be used to differentiate primary LMS from metastasis. Kim et al[8] described an increased expression of oncogenes for cellular proliferation and angiogenesis in metastasized LMS, specifically angiogenin, vascular endothelial growth factor, CD31, and von Willebrand factor. Although Unver et al[45] found that neither p16 nor p21 correlated with disease-free or overall survival in gynecologic LMS, it is generally accepted that p16 is expressed more frequently and more strongly in LMSs compared with leiomyomas and is a useful antibody in discriminating LMSs from leiomyomas.[39]

Interestingly, the present study showed the influence of p16 and p21 expression on the long-term prognosis of this disease. To date, there are no other currently published studies regarding this issue owing to the rarity of LMS in the head and neck region. Further multicenter studies are needed to improve the treatment and prognosis of this sporadic disease and to develop more targeted treatments against metastatic uterine sarcomas.

In conclusion, LMS is an exceedingly rare tumor in the oral and maxillofacial region and has a poor prognosis because of a high local recurrence rate. There

may be a predilection for occurrence in the jawbones, with bone involvement possibly associated with an even poorer prognosis because of a higher recurrence rate. In primary LMS, one third of patients develop distant metastases, with lymph node metastases being less frequent. Distant metastases in the head and neck region originating from the female genitalia must be taken into account in the initial tumor staging; therefore, whole-body imaging and a gynecologic examination are necessary.

Aggressive surgical treatment is necessary for a total cure. Treatment of primary LMS is radical tumor resection with histologically clear margins. When lymph node metastases are suspected, an additional uni- or bilateral neck dissection is indicated, depending on the tumor location. Adjuvant radiation and chemotherapy also may have a beneficial effect in decreasing or delaying the recurrence rate, improving survival time, and sometimes allowing the possibility of less radical resection.

Immunohistochemical markers such as ASMA and vimentin are important for the diagnosis of LMS. They frequently express cyclin kinase inhibitors p16 and p21. Lack of nuclear p16 seems to be associated with a trend toward a poorer prognosis.

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Deutschsprachige Zusammenfassung

1. Einleitung

Leiomyosarkome (LMS) sind sehr seltene Tumoren der glatten Muskulatur, welche am häufigsten im Myometrium des Uterus, im Gastrointestinaltrakt und im Retroperitoneum auftreten [14]. Insgesamt besitzen sie einen Anteil von etwa 7% an allen Weichgewebssarkomen [13]. Weniger als 5% aller Leiomyosarkome manifestieren sich im Kopf-Hals-Bereich, weniger als 0,1% treten in der Mundhöhle auf [36]. Nach dem Ursprungsgewebe können in der oralen und perioralen Region LMS der oralen Weichgewebe, LMS der Gesichtshaut und LMS der Kieferknochen unterschieden werden.

Abzugrenzen von den primären LMS des Kopf-Hals-Bereichs sind sekundäre, metastasierte LMS, am häufigsten ausgehend von den weiblichen Genitalien, insbesondere vom Uterus [21].

Aufgrund des seltenen Auftretens der Tumoren im Kopf-Hals-Bereich ist die histopathologische Diagnose mitunter schwierig. Immunhistochemische Zusatzuntersuchungen, wie etwa die Positivität der Tumoren für Vimentin, Desmin oder SMA (Smooth Muscle Actin) sind von entscheidender Bedeutung [34]. Die Proteine p16 und p21 sind wichtige Regulatoren des Zellzyklus und werden von p53 kontrolliert [8]. P53 ist in Leiomyosarkomen häufig mutiert und immunhistochemisch exprimiert [31], weshalb ein Zusammenhang der Tumorprogression und dem immunhistochemischen Expressionscore von p16 und p21 bestehen könnte. Die Überexpression von p16 scheint Leiomyosarkome von Leiomyomen und seinen benignen Varianten zu unterscheiden [15].

Die vorliegende retrospektive klinisch-pathologische Studie soll

1. das charakteristische klinische Erscheinungsbild der LMS des Kopf-Hals-Bereiches und den Verlauf unter Therapie dokumentieren,
2. eine Analyse der Zellzyklus- assoziierten Proteine p16 und p21 in LMS der Kopf-Hals-Region vorstellen.

2. Patienten und Methoden

Die vorliegende klinisch-pathologische Studie umfasst sieben Patienten mit einem histopathologisch gesicherten Leiomyosarkom des Kopf-Hals-Bereiches, welche in den Jahren 1996 bis 2008 in den Kliniken für Mund-, Kiefer- und Gesichtschirurgie der Universität Regensburg und der Universität Lübeck behandelt wurden. Epidemiologische Daten, Symptome, Therapie und klinischer Verlauf wurden anhand der ambulanten und stationären Patientenakten retrospektiv erhoben.

Von allen Patienten lagen formalinfixierte, in Paraffin eingebettete Gewebeblöcke vor. Zur Analyse wurden gewöhnliche H&E-Färbungen verwandt. Für die immunhistochemischen Marker Vimentin, Desmin, ASMA (Alpha Smooth Muscle Actin) und Ki67 wurden die Ergebnisse der Routinediagnostik übernommen. Die Färbungen für p16 und p21 wurden für alle Tumoren neu angefertigt. Ausgewertet wurde hier der prozentuale Anteil an positiv gefärbten Tumorzellen.

Die Detektion der gebundenen Antikörper erfolgte mit Hilfe des ChemMate Detektionssystems (Alkalische Phosphatase) und eines Immunfärbeautomats (Dako Autostainer, Deutschland) entsprechend dem Protokoll des Herstellers (Tab. 1).

Antikörper	Klon	Hersteller	Verdünnung	Vorbehandlung
P16	E6H4	Mtm Laboratories Deutschland	-	Peroxidase Blockierungssystem pH 9
P21	DSC-60.2	Zytomed Systems Deutschland	1:50	Target Retrieval Solution 1:10 pH 6,1
Vimentin	V9	Dako Deutschland	1:4500	Target Retrieval Solution 1:10 pH 9
Desmin	D33	Dako Deutschland	1:200	Target Retrieval Solution 1:10 pH 9
ASMA	1A4.(1)	Dako Deutschland	1:300	Target Retrieval Solution 1:10 pH 9
Ki67	MIB1	Dako Deutschland	1:1000	Target Retrieval Solution 1:10 pH 6,1

Tabelle 1: In der Studie verwendete primäre Antikörper

3. Ergebnisse

3.1. Klinik

Das Patientenkollektiv umfasste 3 Männer und 4 Frauen mit einem Durchschnittsalter von 60 Jahren (25-93 Jahre), welche an einem LMS des Kopf-Hals-Bereiches erkrankt waren. Bei fünf Patienten hatte sich das LMS primär im Kopf-Hals-Bereich entwickelt (Tab. 2).

Bei zwei Patienten handelte es sich um eine LMS-Metastase mit Primarius im Uterus bzw. Becken.

P	Alter (a)/ Geschlecht	Lokalisation im Kopf-Hals-Bereich	T (cm)	Knochen-infiltration (histologisch)	Primärtherapie bei Erstmanifestation im Kopf-Hals-Bereich	Rezidiv / Metastasen (Monate nach Therapie)	Verlauf (a)
1	75/m	Unterlippe	0,8	nein	Tumorresektion lokal R0	Zervikal(3Mo); submandibulär, supraclaviculäre LK, Lunge (10 Mo)	† 1,6
2	74/w	Wangenhaut	2,5	nein	Tumorresektion lokal R0	Nein	* 4,7
3	39/w	Trigonum retromolare	1,5	ja	Tumorresektion lokal R0.+ zervikale LK-Dissektion + Radiatio 49,6 Gy	Kaumuskulatur (10 Mo) Lunge, Leber, Niere, Knochen, Nebenniere, Magen, Schilddrüse (11 Mo)	† 1,0
4	73/m	Harter/weicher Gaumen	2	nein	Tumorresektion local R0 + zervikale LK-Dissektion	Pharynx,, Gaumen, Kaumuskulatur re (7 Mo) Lunge (28 Mo)	† 2,7
5	25/m	Mundboden	2,5	nein	Tumorresektion lokal R0. + zervikale LK-Dissektion	Nein	* 6,5
6	93/w	Schädelkalotte (Metastase Becken-LMS)	4	ja	Tumorresektion lokal R0	Glandula submandibularis, Lunge (14 Mo)	† 5,3
7	44/w	Sinonasaltrakt (Metasase Uterus-LMS)	n.g.	ja	palliative Radiatio 56 Gy	Lunge (zeitgleich)	† 1,4

P Patient, **a** Jahre, **m** männlich, **w** weiblich, **T** Tumorgröße bei Erstdiagnose, **n.g.** nicht genannt, **Gy** Gray, **R0** kein Residualtumor, **LK** Lymphknoten, † verstorben, * lebend

Tabelle 2: Klinische Daten der untersuchten Patienten

Die Therapie der primären LMS umfasste in beiden Kliniken die Tumorresektion mit histologisch tumorfreien Grenzen. Bei drei Patienten wurde eine prophylaktische Ausräumung der zervikalen Lymphknoten durchgeführt. In einem Fall erfolgte eine postoperative Radiatio. Die LMS-Metastasen im Kopf-Hals-Bereich wurden palliativ bestrahlt bzw. reseziert (Tab. 2).

Drei der fünf Patienten (60%) mit primärem LMS im Kopf-Hals-Bereich entwickelten unabhängig von der gewählten Therapie nach durchschnittlich 7 Monaten (3-10) ein Tumorrezidiv, nach durchschnittlich 17 Monaten (10-29) zusätzlich Lungenmetastasen. Bei einem der beiden Patienten mit solitärer Tumorresektion traten 10 Monate postoperativ Metastasen in den Halslymphknoten auf.

Die LMS des Uterus bzw. Beckens metastasierten in die Keilbeinhöhle und Siebbeinzellen bzw. in den Sinus cavernosus, retroaurikulär und in die mediane Schädelkalotte und bildeten weitere Tochtergeschwülste in der Lunge und der Glandula submandibularis (Tab. 2).

Von insgesamt 7 Patienten waren zum Ende der Auswertung 5 Patienten nach einem durchschnittlichen Überleben von 2,4 Jahren (1,0-5,3) mit stattgefundener Fernmetastasierung verstorben. Zwei Patienten mit einem primären LMS der subkutanen Wangenhaut bzw. des Mundbodens waren zum Abschluss der Auswertung nach 4,7 bzw. 6,5 Jahren ohne Hinweis auf ein Rezidiv oder eine Fernmetastasierung am Leben. (Tab. 2).

Das durchschnittliche Überleben aller Patienten lag zum Ende der Auswertung bei 3,3 Jahren (1,0 - 6,5). Die mittlere Überlebensdauer der fünf Patienten mit einem primären LMS des Kopf-Hals-Bereiches betrug ebenfalls 3.3 Jahre (1,0-6,5)

3.2. Histologie

Die LMS der eigenen Untersuchungsserie zeigten übereinstimmend ein grobknotiges und infiltratives Wuchsbild mit spindeligen oder polygonalen Zellen (Abb. 1a und 1b). Beide Zellformen waren regelmäßig innerhalb eines Tumors sichtbar. Ein Zytoplasmasaum war immer nachweisbar, oft mit feinfibrillärer eosinophiler Textur. Physiologische Mitosen waren immer nachweisbar. Der kollagene Fasergehalt zwischen den Tumorzellen war gering.

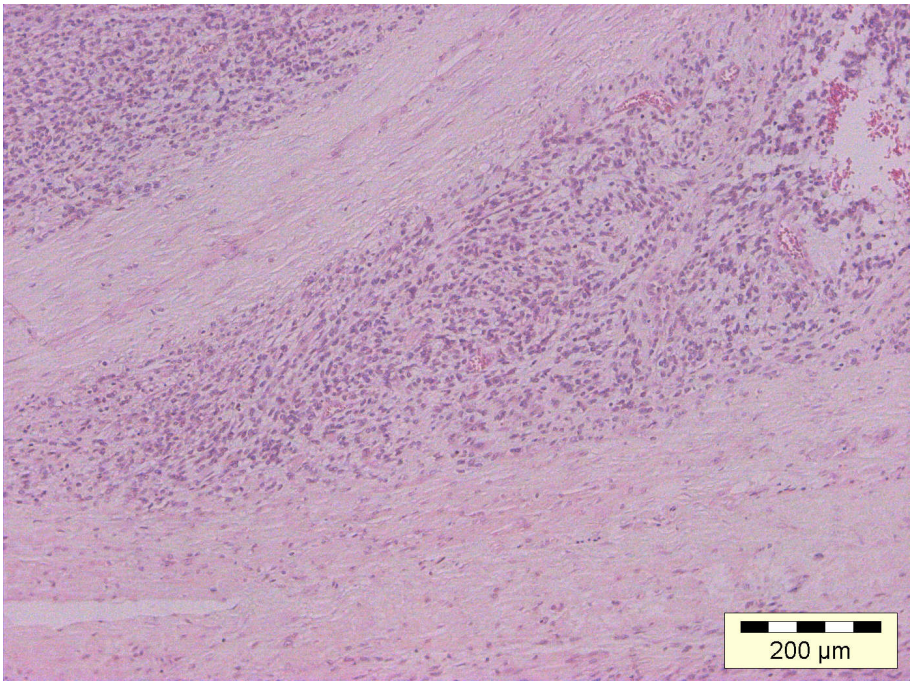

Abbildung 1a: HE-Übersichtsaufnahme: LMS mit grobknotiges Wuchsbild.

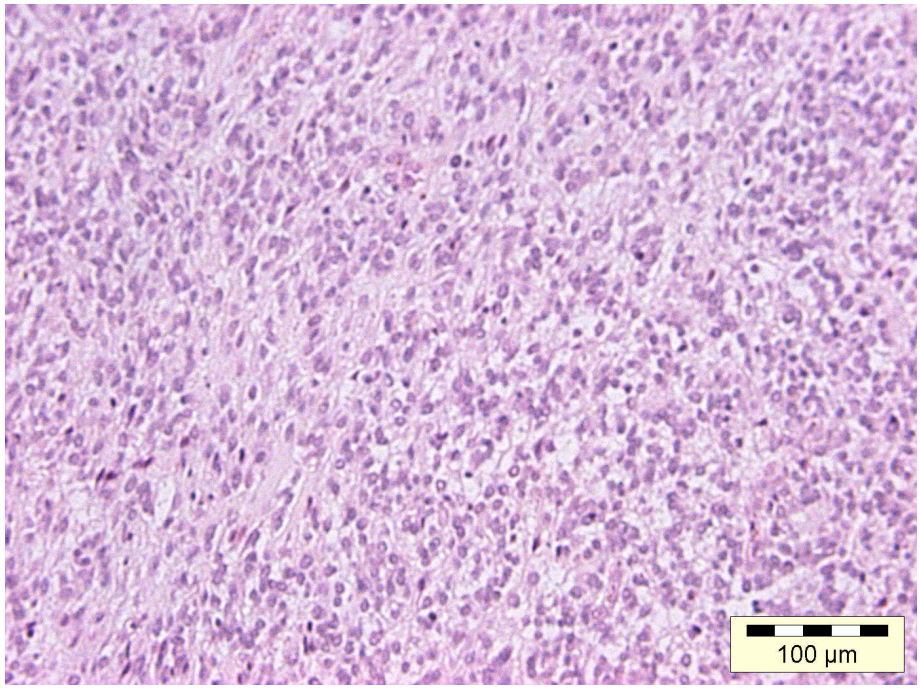

Abbildung 1b: HE-Detailaufnahme: LMS mit spindeligen und runden Tumorzellen; Nachweis einer hohen Mitoseaktivität durch Mitosefiguren.

Immunhistochemisch zeigten sich die Tumorzellen positiv für das Intermediärfilament Vimentin (5/5) und den Muskelmarker ASMA (5/5). 2 von 5 untersuchten Tumoren waren positiv für Desmin (Tab. 3).

P	Primär-lokalisation	Vimentin	Desmin	ASMA	Ki67	p16	p21	Verlauf (a)
1.	Unterlippe	100% pos	Neg	10% pos	50%	Neg	2% pos	† 1,6
2.	Wangenhaut	Pos	Neg	Pos	n.d.	2%	5%	* 4,7
3.	Trigonum retromolare	Pos	Pos	Pos	n.d.	Neg	25%	† 1,0
4	Gaumen	n.d.	n.d.	n.g.	n.d.	100% pos	Neg	† 2,7
5.	Mundboden	Pos	Neg	Pos	n.d.	5%	5%	* 6,5
6.	Becken	n.d.	n.d.	n.d.	n.d.	80%	25%	† 5,3
7.	Uterus	100% pos	2% pos	100% pos	5%	Neg	Neg	† 1,4

P Patient, **a** Jahre, **Pos** positive Färbung, **Neg** negative Färbung, **n.d.** nicht durchgeführt,† verstorben, * lebend

Tabelle 3: Auswertung der immunhistochemischen Färbungen

Bei zwei Tumoren wurde der Proliferationsmarker Ki-67 bestimmt, wobei das LMS der Lippe eine hohe Proliferationrate von 50% aufwies, das primär im Uterus entstandene LMS lediglich eine Proliferationsrate von 5% zeigte. 4 von 7 Proben (57%) exprimierten nukleäres p16 (Abb. 2a).

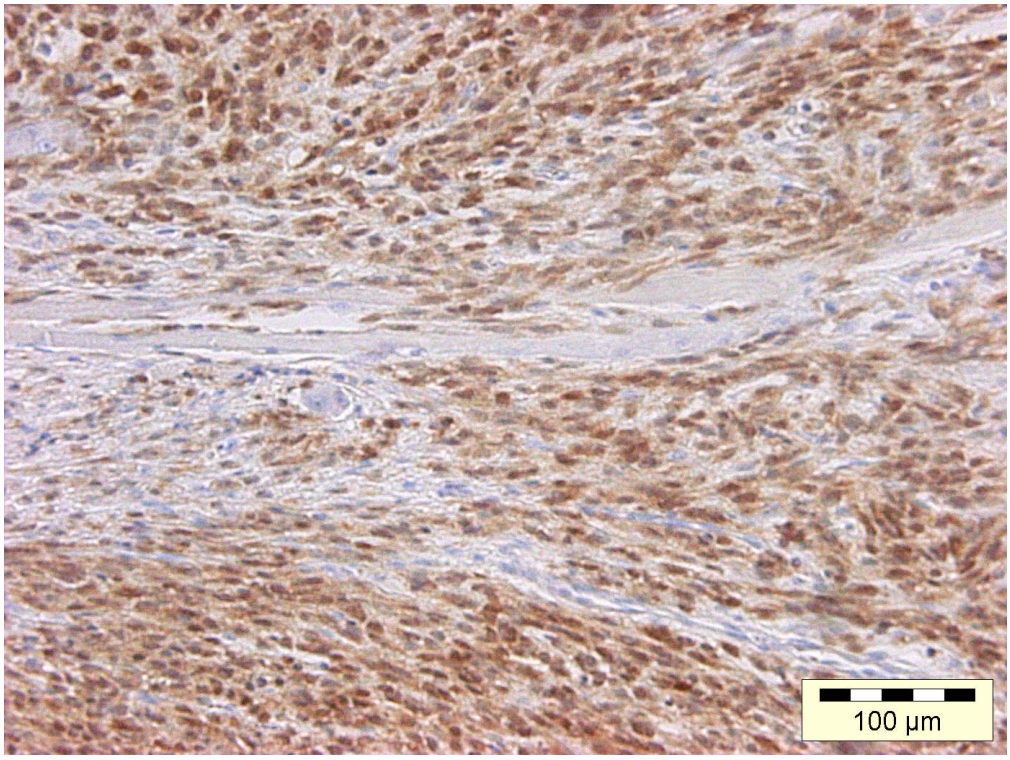

Abbildung 2a: nukleäre Expression von p16 (braunes Signal).

Für diese Patienten lag das durchschnittliche Überleben bei 4,3 Jahren (2,7-6,5). Die Patienten mit Verlust der P16-Expression wiesen hingegen ein durchschnittliches Überleben von 1,3 Jahren (1,0-1,6) auf (Tab. 3). Beide Tumoren der rezidiv- und metastasenfreien Patienten exprimierten p16. 5 von 7 Tumoren (71%) zeigten sich positiv für p21. Hier lag das durchschnittliche Überleben der p21-positiven Fälle bei 3,8 Jahren (1,0-6,5), das der p21-negativen Fälle (Abb. 2b) bei 2,1 Jahren (1,4-2,7).

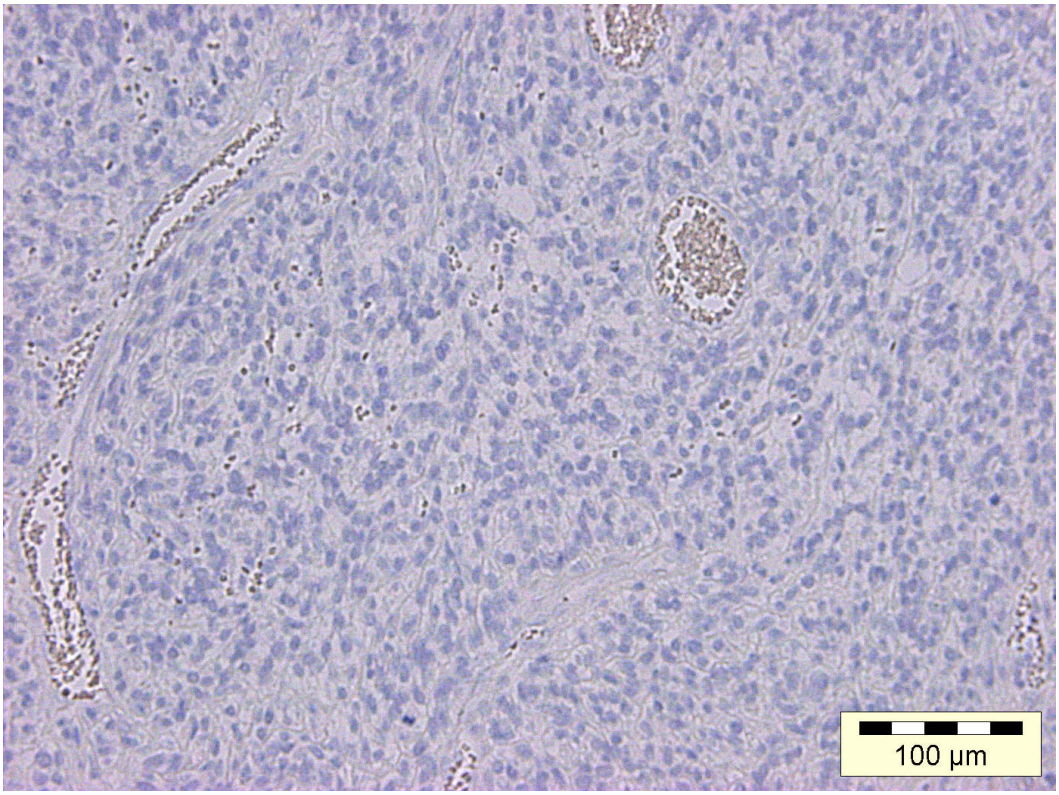

Abbildung 2b: p21 keine Expression

Die Expression der beiden Proteine war nicht miteinander assoziiert. Eine Korrelation mit der Tumorlokalisation des Primarius konnte nicht beobachtet werden. Ebenso wenig ermöglichten die immunhistochemischen Marker eine Differenzieung zwischen primären LMS und LMS-Metastasen.

4. Diskussion

Während Leiomyosarkome sich relativ häufig im Uterus und Gastrointestinatrakt manifestieren [12, 25], entstehen primär im Kopf-Hals-Bereich nur 3% aller LMS [28, 29, 38], da in dieser Region nur wenige glatte Muskelzellen vorliegen. Im Kopf-Hals-Bereich nehmen LMS vermutlich ihren Ursprung in der Tunika media der Arterien, dem Ductus lingualis, den Papillae circumvallatae und den pluripotenten Mesenchymalzellen [4, 38]. Der Sinonasal-Trakt (19%), die Haut und das Weichgewebe (16%) sowie der Ösophagus (12%) bilden hier die Prädilektionsstellen [38].

Angaben zur prognostischen Bedeutung der Lokalisation der primären LMS innerhalb des Kopf-Hals-Bereiches sind nicht kongruent. Die aktuelle WHO-Klassifikation der Tumoren des Weichgewebes und des Knochens beschreibt eine eher schlechte Prognose der primären LMS des Sinonasal-Traktes und eine variable Prognose bei primärem Auftreten des LMS im Larynx [16, 33]. Primäre LMS der oralen und perioralen Weich- und Hartgewebe zeigen in größeren Untersuchungen eine 5-Jahres-Überlebensrate von 32-62% [13, 18, 36] (Tab. 4), wobei LMS der oralen Weichgewebe eine bessere Prognose aufweisen als LMS der Kieferknochen. Bei den eigenen 5 Patienten mit einem primären LMS des Kopf-Hals-Bereiches betrug die mittlere Überlebensdauer 3.3 Jahre (1,0-6,5). Lediglich 2 Patienten (5-JÜR ca. 40%) waren nach 4,7 bzw. 6,5 Jahren noch am Leben. Eine Zuordnung der Prognose zur Tumorlokalisation konnte aufgrund der geringen Fallzahl nicht getroffen werden. In 3 von 5 Fällen (60%) kam es nach durchschnittlich 17 Monaten zu einer Fernmetastasierung in Form von Lungenmetastasen, was über der in der Literatur angegebenen Metastasenwahrscheinlichkeit von etwa 35% für primäre orale LMS liegt [13] (Tab. 4). Die Lunge gilt neben der Leber als Prädilektionsstelle für Fernmetastasen beim LMS des Kopf-Hals-Bereiches [14, 38].

Neben den häufigeren Fernmetastasierungen kann es bei LMS der Kopf-Hals-Region in etwa 15% der Fälle auch zu regionalen Lymphknotenmetastasierungen kommen [11, 13, 28]. In der eigenen Untersuchungsserie kam es bei einem LMS der Unterlippe zu einer Tumorabsiedelung in die Halslymphknoten.

Bezüglich der Rezidivhäufigket wird für primäre LMS der oralen Weichgewebe eine Rezidivrate von etwa 35% angegeben [13] (Tab. 4), was der Rezidivhäufigkeit von 43% in der eigenen Untersuchung entspricht.

Quelle	Patien-ten (a)	M: w	Alter (a)	Primärlokalisation (n)	Therapie (n)	Rezidiv (%)	Fernmetastasen (%)	Verlauf nach Therapie
Carter et al. (1999) [ ]	11	1,2 :1	40	Kieferknochen (11)	OP (10), RT (3), CT (2)	n.g.	36	† 36% nach 36 Mo, * 36% o T nach 12 Mo, * 18 m T nach 24 Mo
Dry et al. (2000) [ ]	10	1: 1,5	34	Kieferknochen (5), Orale Weichgewebe (5)	OP (9), RT (1), CT (2), unbekannt (1)	20	33	† 50% nach 20 Mo, * 40% o.T. nach 49 Mo
Ethunandan et al. (2007) [ ]	64	1,3: 1	43	Kieferknochen (38), Orale Weichgewebe (20), Gesichtshaut (6)	OP (60), RT (14), CT (11)	34	35	5-JÜR 55% gesamt, 43% bei Knocheninfiltration, 19% bei Metastasen
Izumi et al. (1995) [ ]	60	1,4 : 1	42	Kieferknochen (27), Sinus maxilaris (14), Orale Weichgewebe (18), Gesichtshaut (1)	OP (55), RT (4), CT (39), unbekannt (2)	44	35	2-JÜR 66%, 5 JÜR 32% gesamt
Kratochvil et al. (1982) [ ]	20	4:1	65-70	Kieferknochen (8) Skelettknochen (12)	OP (18), RT (6), CT (2)	n.g.	37	† 35% nach 24 Mo, * 45% nach 21 Mo, 20% n.g.
Montgomery et al. (2002) [ ]	13	1,2 :1	47	Kieferknochen (5), Orale Weichgewebe (3) Gesichtshaut (2), Halsmuskulatur (2), Pharynx (1)	OP (9), unbekannt (4)	27	55	† 23% nach 67 Mo, * 38% o.T. nach 50 Mo, * 8% m.T. nach 24 Mo 31% n.g.
Vilos et al. (2005) [ ]	50	1: 1,3	44	Kieferknochen (34), Orale Weichgewebe (15), Sinus Max. (1)	OP (46), RT (14), CT (13) unbekannt (4)	n.g.	32	5-JÜR 62%
Eigene Studie	7	1 : 1,3	60	Orale Weichgewebe (4), Gesichtshaut (1), Metastasen (2)	OP (6), RT (2)	43	71	† 71% nach 29 Mo * 29% o. T. nach 67 Mo

a Jahr, **m** männlich, **w** weiblich, **OP** Operation, **RT** Radiatio, **CT** Chemotherapie, * lebend, † gestorben, **o.T.** ohne Tumor, **m.T.** mit Tumor, **Mo** Monate, **JÜR** Jahresüberlebensrate, **n.g.** nicht genannt

Tabelle 4: Literaturübersicht zur Epidemiologie, zur Therapie und zum klinischen Verlauf primärer Leiomyosarkome des Kopf-Halsbereiches

Wenn auch selten, so ist bei einem LMS im Kopf-Hals-Bereich dennoch die Möglichkeit eines fernmetastasierten Tumors in Erwägung zu ziehen (Tab. 5). Als Primärlokalisation zeigt sich hier vor allem der Uterus, was eine präoperative gynäkologische Untersuchung empfehlen lässt.

Quelle	Alter (a)	Geschlecht	Primär-lokalisation	Lokalisation Metastase	Therapie	Verlauf (a)
Allen et al. (1993) [ ]	66	M	Bein	Harter Gaumen	OP+RT+CT	† 2
Allen et al. (1993) [ ]	61	M	Oberschenkel	Unterkiefer	OP+RT+CT	* 3
Allen et al. (1993) [ ]	65	W	Uterus	Unterlippe	OP+CT	* 1,4
Aslan et al. (2008) [ ]	76	W	Uterus	M. temporalis	OP-RT	* 3
Bogart et al. (1990) []	58	W	Lunge	Gaumen	CH+RT	† 0,4
Kaziro et al. (1981) []	59	W	Uterus	Zunge	Keine	Unbekannt
Nusrath et al. (2006) [ ]	65	W	Uterus	M.masseter	OP+CT	† 2,3
Sandruck et al. (2004) [ ]	39	W	Uterus	Sinus sphenoidalis	OP+CT+RT	† 1,1
Uchino et al. (1996) [ ]	54	W	Uterus	Schädel	OP+CT	† 2
Kim et al. (2009) []	56	W	Uterus	Maxilla re	Keine	† 0,3
Vora and Levin (2003) []	62	W	Uterus	Zunge	Keine	† n.g.
Eigene Studie	44	W	Uterus	Sinonasal Trakt	OP+RT	† 1,4
Eigene Studie	93	W	Becken	Schädelkalotte	OP+RT	† 5,3

a Jahre, **w** weiblich, **m** männlich, **Op** Operation, **RT** Radiatio, **CT** Chemotherapie, * lebend, † verstorben, **M** Metastasen, **n.g.** nicht genannt

Tabelle 5: Literaturübersicht zum klinischen Verlauf von in den Kopf-Hals-Bereich metastasierten Leiomyosarkomen

Als entscheidend für die Prognose gilt bei allen primären LMS die weit im Gesunden erfolgte chirurgische Resektion mit histologisch gesicherten, tumorfreien Randschnitten [2, 24, 26, 27]. Eine Chemotherapie bleibt üblicherweise palliativen Situationen - wie inoperablen Primärtumoren oder bereits erfolgter Metastasierng - vorbehalten [11, 13, 24, 28]. Gegenüber der Radiatio erweisen sich sowohl primäre LMS als auch LMS-Metastasen in der Regel als resistent [11, 13, 28, 29]. Auch in der eigenen Studie konnte die Radiatio weder beim Primärtumor noch bei den Tumormetastasen eine Remission erzielen.

Die immunhistochemischen Marker ASMA und Vimentin stellen ein wichtiges Hilfsmittel zur Diagnose eines Leiomyosarkoms dar, was in der eigenen Untersuchung bestätigt werden konnte. Hingegen zeigte sich Desmin nur in 40% der Fälle als positiv. Die Ki67-Proliferationsrate wurde nur in 2 Fällen untersucht (5% und 50%). In der Regel liegt die Zellproliferationsrate von LMS bei über 15% [34].

Das Tumor-Suppressor-Protein p16 reguliert den Zellzyklus in der G1-Phase, indem es den Cyclin D-abhängigen Kinasekomplex 4/6 und somit die Zellproliferation hemmt [23]. Eine verringerte p16-Expression wurde in 5-33% von LMS beobachtet [9, 17]. Verlust an nukleärer P16-Expression in neoplastischen Zellen scheint beim LMS der Weichgewebe mit fortgeschrittener Tumorgröße und schlechterem Gesamtüberleben assoziiert [19].

In der eigenen Untersuchung zeigte sich in 4 von 7 Fällen eine nukleäre Expression von p16. Während die p16-negativen Fälle ein durchschnittliches Überleben von 1,3 Jahren aufwiesen, lag das durchschnittliche Überleben der p16-positiven Fälle bei 4,3 Jahren, was auf eine Prognoseverschlechterung durch p16-Verlust hindeutet.

Bei p21 handelt es sich ebenfalls um ein Cyclin-Kinase-Inhibitor-Protein. Reguliert durch den Tumorsuppressor p53 führt p21 zum Zellzyklusarrest und besitzt eine wichtige

Funktion bei der Reparatur von DNA-Schäden [1, 39]. Leiomyosarkome der Weichgewebe exprimieren üblicherweise p21, wobei der Verlust der p21-Expression mit einem erhöhten Rezidivrisiko einherzugehen scheint [10]. Zwar lag auch in der vorliegenden Studie das durchschnittliche Gesamtüberleben der p21-negativen Fälle (2,1 Jahre) im Vergleich zu den p21-positiven Fällen (3,8 Jahre) niedriger, eine prognostische Aussage bezüglich Rezidiv- oder Gesamtüberlebenswahrscheinlichkeit lässt hier jedoch nicht treffen. Eine Differenzierung zwischen primären LMS und LMS-Metastasen war weder durch p16 noch durch p21 erkennbar. Kim et al. beschreiben in den metastasierten LMS eine erhöhte Expression an Onkogenen für die zelluläre Proliferation und die Angiogenese, etwa Angiogenin, VEGF, CD 31 und vWF [21].

5. Schlussfolgerungen

1. Primäre Leiomyosarkome des Kopf-Hals-Bereiches lassen Fernmetastasen, v.a. in die Lunge, bei jedem dritten Patienten erwarten. Regionäre Lymphknotenmetastasen sind seltener, können aber ebenfalls auftreten. In Betracht zu ziehen ist immer die Metastasierung eines LMS in den Kopf-Hals-Bereich. Als Primarius findet sich hier häufig der Uterus. Ein umfassendes präoperatives Ganzkörper-Staging inklusive gynäkologischer Abklärung ist daher zu empfehlen.
2. Die Therapie von LMS im Kopf-Hals-Bereich besteht in der radikalen chirurgischen Entfernung des Tumors. Bei Verdacht auf Lymphknotenmetastasen sollten diese mit exstirpiert werden. Die Strahlentherapie scheint hingegen keinen großen therapeutischen Wert zu besitzen.
3. Die immunhistochemischen Marker Vimentin und ASMA unterstützen die Diagnostik

eins Leiomyosarkoms. LMS exprimieren häufig die Cyclinkinase-Inhibitoren p16 und p21. Der Verlust von nukleärem p16 scheint mit einer schlechteren Prognose assoziiert.

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