Am J Otolaryngol 40 (2019) 289–291

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Radiotherapy for parapharyngeal space tumors☆

William M. Mendenhall[a,*], Primoz Strojan[b], Jonathan J. Beitler[c], Johannes A. Langendijk[d], Carlos Suarez[e,f], Anne W. Lee[g], Alessandra Rinaldo[h], Juan P. Rodrigo[e,f], Robert Smee[i], Avraham Eisbruch[j], Louis B. Harrison[k], June Corry[l], Alfio Ferlito[m]

[a] Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, USA
[b] Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia
[c] Department of Radiation Oncology, Emory University School of Medicine, Atlanta, GA, USA
[d] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[e] Instituto de Investigación Sanitaria del Principado de Asturias and CIBERONC, ISCIII, Oviedo, Spain
[f] The Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, Oviedo, Spain
[g] Department of Clinical Oncology, University of Hong Kong and University of Hong Kong Shenzhen Hospital, Hong Kong, China
[h] University of Udine, School of Medicine, Udine, Italy
[i] Department of Radiation Oncology, The Prince of Wales Cancer Centre, Sydney, New South Wales, Australia
[j] Department of Radiation Oncology, University of Michigan Medicine, Ann Arbor, MI, USA
[k] Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL, USA
[l] GenesisCare Radiation Oncology Centre at St. Vincent's Hospital, Melbourne, Australia
[m] Coordinator of the International Head and Neck Scientific Group, Padua, Italy

ARTICLE INFO

Keywords:
Radiotherapy
Head and neck cancer
Parapharyngeal space tumors
Paraganglioma
Schwannoma
Soft-tissue sarcoma

ABSTRACT

A wide variety of tumors, both benign and malignant, occur in the parapharyngeal space. Depending on histology and extent, treatment may include surgery and/or radiotherapy (RT). Herein we discuss the role of RT in the management of some of the more commonly encountered neoplasms, including salivary gland tumors, paragangliomas, schwannomas, and soft-tissue sarcomas.

1. Introduction

Radiation therapy (RT) for parapharyngeal space (PPS) tumors is technically demanding owing to the complex anatomic setting combined with the histological diversity of tumors that may appear in this part of the body. In most cases, the treatment of choice is surgical resection, and the role of surgery – including possible approaches with related complications and oncological outcomes – has been extensively described in several publications [1–3]. The goal of this paper is to discuss the role of RT for these PPS tumors.

Tumors in the PPS represent only 0.5% of all head and neck tumors and most PPS tumors (80%) are benign [4]. Primary masses originate from the anatomical structures situated in this compartment, but a PPS tumor can also be a metastasis or extension from a tumor in an adjacent anatomical structure. Up to 70 different histological subtypes of PPS tumors exist, including minor salivary gland neoplasms, neurogenic neoplasms, and soft-tissue sarcomas (STS). Recently, van Hees et al. reported on 99 patients treated for PPS tumors between 1991 and 2012 at the VU University Medical Center (Amsterdam) and observed that 49.5% were salivary gland neoplasms, 41% were neurogenic, and 9% had a different origin [3]. Pleomorphic adenomas and paragangliomas (PGs) were the two most frequently reported histological types, in 31% and 30% of the cases, respectively.

External-beam RT is usually administered in the postoperative setting. Indications for postoperative radiation include aggressive, malignant histology as well as inadequate margins. Primary RT may be considered for patients who are felt unsuitable for surgery because of poor health, pre-existing contralateral deficit(s) of the vagal and/or hypoglossal nerves (with consequent risk of bilateral neurological deficits resulting in airway and swallowing problems), or the lesion is unresectable (e.g., infiltration of the internal carotid artery) [1]. Another possible indication for primary RT includes a benign histology for

☆ This article was written by members of the International Head and Neck Scientific Group (www.IHNSG.com).

* Corresponding author: 2000 SW Archer Rd., PO Box 100385, Gainesville, FL 32610-0385, USA.
E-mail address: mendwm@shands.ufl.edu (W.M. Mendenhall).

https://doi.org/10.1016/j.amjoto.2018.12.010
Received 2 November 2018

which RT would potentially lower the probability of treatment-related complications compared to surgery while achieving comparable local control [1,5]. Slow-growing tumors like vagal PGs or vagal neuromas may fall into this category. Discussion of the role of RT for the treatment of various non-Hodgkin lymphomas and pediatric sarcomas that can although rarely arise in the PPS is beyond the scope of this paper. Some cases may require interdigitation of chemotherapy, surgery, and external RT, but these choices are often best worked out in a multidisciplinary tumor board.

Because of their deep location in the neck, PPS tumors usually reach a considerable size – 2.5 to 3 cm or more – before becoming palpable and diagnosed [6]. RT for PPS tumors is guided not only by tumor histology but also by the extent of the lesion and neighboring anatomical regions in the upper neck and base of skull. Pyramidal in shape, with its base at the skull base, the PPS abuts the carotid canal, the jugular foramen, and the hypoglossal foramen. Whereas the prestyloid compartment contains mostly fat, the retromandibular portion of the parotid gland, and some lymph nodes, the retrostyloid compartment is penetrated by several important structures, including the internal carotid artery (ICA), internal jugular vein (IJV), lower cranial nerves (IX–XII), and the sympathetic chain [4]. In locally advanced lesions invading neighboring structures and penetrating the cranial fossa, the risk of RT-induced damage should be carefully weighed against the probability of cure as treatment may well impact the patient's quality of life.

1.1. Salivary gland neoplasms

Salivary gland neoplasms represent approximately half of all tumors that appear in the PPS and 80% of them are benign. Pleomorphic adenoma is the most common histological type (50%) followed by other benign histologies (30%, including Warthin tumor, basal cell adenoma, and myoepithelioma, to name a few). Only 20% of salivary gland tumors are malignant and the most common malignant salivary gland cancers in the PPS are adenoid cystic carcinoma (9%) and mucoepidermoid carcinoma (5%) [1,3].

The mainstay of treatment for all salivary gland tumors is surgery provided that at least a gross total resection can be achieved [7]. Benign tumors and low-grade carcinomas are treated with surgery alone if negative margins can be achieved, which may be difficult when the primary site is the PPS. Reasons to add postoperative RT include positive margins and local recurrence after prior surgery, particularly if the recurrence is multifocal. Tumor spillage is not a reason to add postoperative RT, at least not for benign tumors. The postoperative dose fractionation schedule used for benign tumors is 60 to 66 for close or positive margins and 70 Gy when treating macroscopic tumor, although the chance for cure of extensive benign tumor masses with RT alone is less likely. The dose per fraction is usually 2 Gy, once daily, 5 days per week in a continuous course. Patients with high-grade carcinomas receive postoperative RT to 60 Gy even if margins are found to be negative. Patients with unresectable tumors are treated with RT alone. The value of particle therapy (protons or carbon ions) in the treatment of salivary gland tumors, benign and malignant, is now under extensive evaluation, not only due to a more favorable toxicity profile compared to photon-beam irradiation but also because of the higher biological effectiveness of different particle beams [8]. This is especially the case for unresectable adenoid cystic carcinoma, where carbon ion therapy provides higher local control rates than those observed after conventional photon-based radiotherapy [9,10]. There is no established role for adjuvant chemotherapy for salivary gland malignancies [10].

1.2. Paragangliomas

PGs are uncommon neuroendocrine tumors that are thought to arise from paraganglia and are usually found in the head and neck. The vagal PG is, depending on the series, the second or third most common tumor diagnosed in the PPS. However, the sympathetic chain and ICA traversing the PPS can also be sites of origin for these tumors. Fewer than 10 to 20% of PGs are malignant, mainly vagal PGs harboring a germinal mutation in the SHDB gene. Malignancy cannot be distinguished by histology but rather by the presence of regional or distant metastases. Less than 5% of PGs are metabolically active and produce catecholamines. A minority of patients have familial PGs related to mutations of the succinate dehydrogenase genes and tend to present at a younger age and with multiple PGs. They can be bilateral in 10% of sporadic cases and 25% of hereditary cases [11,12].

Management of patients with PGs depends on the location and extent of the lesion(s) and the medical condition of the patient. Elderly, asymptomatic patients with a limited life expectancy may be observed with follow-up computed tomography or magnetic resonance imaging scans obtained annually. Patients with small jugular PGs that are amenable to complete resection with minimal functional deficits may be treated surgically. Concerning vagal PGs, only malignant tumors or those with a complete preoperative vagal palsy should be submitted to surgery [12]. The main argument against surgical intervention is the high rate of incomplete resections or recurrences and, more importantly, the high rate of morbidity [12]. In surgical series, the vagus nerve has been functionally preserved in fewer than 10% of the patients. Planned subtotal resection should not be performed since it does not improve local control over RT alone yet significantly increases the risk of morbidity. Skull base PGs that are 3 cm or smaller in maximum diameter are suitable for stereotactic radiosurgery (SRS). Local control after SRS or fractionated RT is defined as stability or gradual regression; benign tumors rarely regress completely. So long as the tumor does not progress, the tumor is unlikely to cause additional morbidity. The SRS dose is 12.5 Gy in 1 fraction specified at the tumor margins [11]. The advantage of SRS versus fractionated RT is convenience (the entire procedure, including preparation and treatment execution, is completed in one day) and its disadvantages include a slightly higher risk of a marginal miss and a cranial neuropathy due to the high dose delivered per fraction. Patients may also be treated with fractionated RT to 45 Gy in 25 fractions over 5 weeks. Although less convenient, the likelihood of cure is excellent and the morbidity with this dose level is minimal, particularly if treated with intensity-modulated RT (IMRT) [12,13]. The likelihood of long term local after RT or SRS is approximately 90% or higher [13]. Although unclear, the optimal treatment of patients with malignant PGs is probably complete resection followed by postoperative RT using total doses in the range of 65 to 70 Gy [14,15].

1.3. Schwannomas

Schwannomas are benign, slow growing neoplasms of neuroendocrine origin that occur in the skull base, and may originatefrom the 8th cranial verve. Less than 1% of benign schwanommas undergo malignant transformation. Possible sites of origin of schwanommas include the retrostyloid part of the PPS, along the course of the vagal nerve, as well as long cranial nerves IX, XI, and XII. Their average growth rate is 1 to 2 mm per year [16,17].

Treatment options include observation, surgery, SRS, and fractionated RT. A “wait and see” policy may be a reasonable option for patients who are asymptomatic and have a limited life expectancy. Surgery is an appropriate option for patients with schwannomas 3 cm or larger in maximum diameter that appear to be completely resectable with an acceptable functional outcome, principally if the patients have developed a preoperative lower cranial nerves palsy. SRS is a suitable option for patients with smaller tumors, 3 cm or less in maximum diameter, and involving the skull base. The optimal SRS dose is approximately 12.5 Gy specified at the gross tumor volume and may be delivered with a Gamma Knife (Elekta, Stockholm), linear accelerator-based system, or protons with similar outcomes [16,18]. The advantages of SRS over surgery are that it is of comparable effectiveness, is more convenient to the patient, and causes less morbidity. Compared

to fractionated RT, there is likely a higher risk of a cranial nerve injury with SRS and it is not appropriate for tumors below the skull base because of possible motion during treatment. Fractionated RT can be used for PPS schwannomas of any size. The optimal dose-fractionation schedule is approximately 50.4 Gy in 28 fractions [16]. Most of the outcomes data for the treatment of schwannomas are based on vestibular schwannomas. However, it is likely that the local control rates after various treatment modalities for vestibular schwannomas resemble those of tumors arising in other locations and reach 90% or more at 5 years [16,18–20]. Also, in patients with small lesions, quality of life was found similar, irrespective of management by observation, RT, or microsurgery [21].

1.4. Soft-tissue sarcomas

STS are relatively rare, heterogeneous malignancies that usually arise in the extremities and trunk [22]. Kattan et al. reported on 2136 patients treated at the Memorial Sloan Kettering Cancer Center (New York); 4% of patients had head-and-neck STS [23]. STS in the PPF is even more rare.

For the sake of simplicity, STS are classified as either low-grade or high-grade. Once again, the optimal treatment is surgery; the adequacy of the margin is determined by grade [22,24]. Because of the constraints of resecting STS arising in the PPS, margins are rarely ideal. Thus, many STS arising in this location require adjuvant RT, depending on extent and grade. Low-grade STS that appear to be resectable with wide margins are treated surgically and postoperative RT is added for close or positive margins. The dose-fractionation schedules are the same as those employed for carcinomas. High-grade STS are treated with either preoperative or postoperative RT; the dose for preoperative RT is approximately 50 Gy in 25 fractions. Those unsuitable for a gross total resection are treated with RT alone. Recently, encouraging results have been reported with particle therapy [25].

In a series of 319 patients with STS of the head and neck treated during between 1982 and 2012 at the Memorial Sloan Kettering Cancer Center, the reported 4-year overall survival, disease-specific survival, and recurrence-free survival rates were 72%, 76%, and 71%, respectively [26]. Trifiletti et al. reported on 24 adult patients with head-and-neck STS treated with surgery and postoperative RT at the University of Florida between 1981 and 2009 [27]. Patients with rhabdomyosarcomas, Ewing sarcoma, or angiosarcomas were not included. All patients underwent a gross total resection and postoperative RT. After a median follow-up of 11 years, the local control and progression-free survival rates were 83% at 5 years and 73% at 10 years. All recurrences were local and no patient with a recurrence was salvaged [27].

2. Conclusion

A wide variety of benign and malignant tumors arise in the PPS. The optimal treatment depends on histology, tumor extent, and the medical condition of the patient. RT alone or combined with surgery is an important component of the management of many of these patients.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding

None.

References

[1] López F, Suárez C, Vander Poorten V, Mäkitie A, Nixon IJ, Strojan P, et al. Contemporary management of primary parapharyngeal space tumors. Head Neck 2018. https://doi.org/10.1002/hed.25439.
[2] Riffat F, Dwivedi RC, Palme C, Fish B, Jani P. A systematic review of 1143 parapharyngeal space tumors reported over 20 years. Oral Oncol 2014;50:421–30. https://doi.org/10.1016/j.oraloncology.2014.02.007.
[3] van Hees T, van Weert S, Witte B, Rene Leemans C. Tumors of the parapharyngeal space: the VU University Medical Center experience over a 20-year period. Eur Arch Otorhinolaryngol 2018;275:967–72. https://doi.org/10.1007/s00405-018-4891-x.
[4] Maheshwar AA, Kim EY, Pensak ML, Keller JT. Roof of the parapharyngeal space: defining its boundaries and clinical implications. Ann Otol Rhinol Laryngol 2004;113:283–8. https://doi.org/10.1177/000348940411300405.
[5] Suarez C, Fernandez-Alvarez V, Neumann HP, Boedeker CC, Offergeld C, Rinaldo A, et al. Modern trends in the management of head and neck paragangliomas. Eur Arch Otorhinolaryngol 2015;272:3595–9. https://doi.org/10.1007/s00405-015-3793-4.
[6] Som PM, Biller HF, Lawson W, Sacher M, Lanzieri CF. Parapharyngeal space masses: an updated protocol based upon 104 cases. Radiology 1984;153:149–56. https://doi.org/10.1148/radiology.153.1.6089262.
[7] Holtzman A, Morris CG, Amdur RJ, Dziegielewski PT, Boyce B, Mendenhall WM. Outcomes after primary or adjuvant radiotherapy for salivary gland carcinoma. Acta Oncol (Stockh) 2017;56:484–9. https://doi.org/10.1080/0284186x.2016.1253863.
[8] Orlandi E, Iacovelli NA, Bonora M, Cavallo A, Fossati P. Salivary gland. Photon beam and particle radiotherapy: present and future. Oral Oncol 2016;60:146–56. https://doi.org/10.1016/j.oraloncology.2016.06.019.
[9] Jensen AD, Nikoghosyan AV, Poulakis M, Hoss A, Haberer T, Jakel O, et al. Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival. Cancer 2015;121:3001–9. https://doi.org/10.1002/cncr.29443.
[10] Sulaiman NS, Demizu Y, Koto M, Saitoh JI, Suefuji H, Tsuji H, et al. Multicenter study of carbon-ion radiation therapy for adenoid cystic carcinoma of the head and neck: subanalysis of the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS) study (1402 HN). Int J Radiat Oncol Biol Phys 2018;100:639–46. [doi:S0360-3016(17)34098-1 [pii] 11.1016/j.ijrobp.2017.11.010].
[11] Mendenhall WM, Amdur RJ, Vaysberg M, Mendenhall CM, Werning JW. Head and neck paragangliomas. Head Neck 2011;33:1530–4. https://doi.org/10.1002/hed.21524.
[12] Suarez C, Rodrigo JP, Bodeker CC, Llorente JL, Silver CE, Jansen JC, et al. Jugular and vagal paragangliomas: systematic study of management with surgery and radiotherapy. Head Neck 2013;35:1195–204. https://doi.org/10.1002/hed.22976.
[13] Gilbo P, Morris CG, Amdur RJ, Werning JW, Dziegielewski PT, Kirwan J, et al. Radiotherapy for benign head and neck paragangliomas: a 45-year experience. Cancer 2014;120:3738–43. https://doi.org/10.1002/cncr.28923.
[14] Sethi RV, Sethi RK, Herr MW, Deschler DG. Malignant head and neck paragangliomas: treatment efficacy and prognostic indicators. Am J Otolaryngol 2013;34:431–8. https://doi.org/10.1016/j.amjoto.2013.03.010.
[15] Gilbo P, Tariq A, Morris CG, Mendenhall WM. External-beam radiation therapy for malignant paraganglioma of the head and neck. Am J Otolaryngol 2015;36:692–6. https://doi.org/10.1016/j.amjoto.2015.06.004.
[16] Mendenhall WM, Friedman WA, Amdur RJ, Antonelli PJ. Management of acoustic schwannoma. Am J Otolaryngol 2004;25:38–47. [doi:].
[17] Zou J, Hirvonen T. “Wait and scan” management of patients with vestibular schwannoma and the relevance of non-contrast MRI in the follow-up. J Otolaryngol 2017;12:174–84. https://doi.org/10.1016/j.joto.2017.08.002.
[18] Friedman WA. Linear accelerator radiosurgery for vestibular schwannomas. Prog Neurol Surg 2008;21:228–37. https://doi.org/10.1159/000157171.
[19] Woolf DK, Williams M, Goh CL, Henderson DR, Menashy RV, Simpson N, et al. Fractionated stereotactic radiotherapy for acoustic neuromas: long-term outcomes. Clin Oncol (R Coll Radiol) 2013;25:734–8. https://doi.org/10.1016/j.clon.2013.08.002.
[20] Kimball MM, Foote KD, Bova FJ, Chi YY, Friedman WA. Linear accelerator radiosurgery for nonvestibular schwannomas. Neurosurgery 2011;68:974–84. discussion 84 https://doi.org/10.1227/NEU.0b013e318208f3a1.
[21] Deberge S, Meyer A, Le Pabic E, Peigne L, Morandi X, Godey B. Quality of life in the management of small vestibular schwannomas: observation, radiotherapy and microsurgery. Clin Otolaryngol 2018. https://doi.org/10.1111/coa.13203.
[22] Mendenhall WM, Indelicato DJ, Scarborough MT, Zlotecki RA, Gibbs CP, Mendenhall NP, et al. The management of adult soft tissue sarcomas. Am J Clin Oncol 2009;32:436–42. https://doi.org/10.1097/COC.0b013e318173a54f.
[23] Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002;20:791–6. https://doi.org/10.1200/jco.2002.20.3.791.
[24] Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res 1980:106–20. [doi:].
[25] Frisch S, Timmermann B. The evolving role of proton beam therapy for sarcomas. Clin Oncol (R Coll Radiol) 2017;29:500–6. https://doi.org/10.1016/j.clon.2017.04.034.
[26] Shuman AG, Brennan MF, Palmer FL, Kuk D, Moraco N, Singer S, et al. Soft tissue sarcoma of the head & neck: nomogram validation and analysis of staging systems. J Surg Oncol 2015;111:690–5. https://doi.org/10.1002/jso.23868.
[27] Trifiletti D, Amdur RJ, Dagan R, Indelicato DJ, Mendenhall WM, Kirwan JM, et al. Radiotherapy following gross total resection of adult soft tissue sarcoma of the head and neck. Pract Radiat Oncol 2012;2. https://doi.org/10.1016/j.prro.2012.01.003. [e121-e8].