Salivary Gland Tumors: Radiotherapy

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Abbreviations

3DRT	3-dimensional conformal radiation therapy
ACC	Adenoid cystic carcinoma
AciCC	Acinic cell carcinoma
CRT	Chemoradiotherapy
CT	Chemotherapy
CXPA	Ex pleomorphic adenoma
DFS	Disease-free survival
DSS	Disease-specific survival
ECE	Extracapsular extension
END	Elective neck dissection
ENI	Elective neck irradiation
HG	High grade
IG	Intermediate grade
IMRT	Intensity-modulated radiation therapy
LC	Local control
LF	Local failure
LG	Low grade
LGSGTs	Low-grade salivary glands cancers
LRC	Locoregional control
MEC	Mucoepidermoid carcinoma

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L. Licitra, L. D. Locati (eds.), *Salivary Gland Cancer*,
https://doi.org/10.1007/978-3-030-02958-6_11

OS	Overall survival
PLGA	Polymorphous low-grade adenocarcinoma
PNI	Perineural involvement
PORT	Postoperative radiation therapy
RFS	Recurrence-free survival
RT	Radiotherapy
SBRT	Stereotactic radiotherapy
SEER	Surveillance, epidemiology, and end results
SGTs	Salivary gland tumors
SOR	Standards, options, and recommendations
VMAT	Volumetric modulated arc therapy

11.1 Introduction

SGTs are rare diseases, accounting for 2–6.5% of all head and neck cancers, and characterized by considerable heterogeneity in their histology, biology, and clinical behavior [1]. Mucoepidermoid carcinoma (MEC), ACC, and adenocarcinoma, NOS, are the most frequent diagnoses, representing >70% of all SGTs, although their frequency varies depending on the site of origin (major vs minor salivary glands) [2]. Among benign lesions, the most common tumor is the pleomorphic adenoma, although it shows great histopathological diversity with a relative proportion of malignancy increasing in smaller glands [3].

Prognosis depends on histology and grading: among non-ACC, high-grade carcinomas are associated with a poorer prognosis compared with low-grade carcinomas [4, 5]. ACC frequently displays an indolent course with a propensity for local or distant recurrence, in particular up to 10–15 years after initial treatment, and it is often highly fatal. Histology, involved gland, and location within the gland have a pivotal role in choosing the best therapeutic management. Complete surgical resection with adequate free margins is the mainstay of treatment for resectable cases. Small, well-localized, low-grade carcinomas excised with clear margins are best treated with surgery alone [2]. PORT is recommended in high-risk patients when adverse prognostic factors based on pathology (T3–T4, lymph node involvement, close/microscopically positive margins, vascular/perineural invasion, and high-grade) can be identified [2]. Unresectable or inoperable SGTs can be managed with RT alone, even though curative purposes are hardly achievable [2].

Overall, SGTs represent a major challenge for the radiation oncologists' community not only for their historically known radioresistance but also for frequently horseshoe-shaped target volume (e.g., in case of perineural invasion) and their proximity to radiosensitive normal structures (e.g., tumors arising from minor salivary glands in paranasal sinuses).

The last two decades has seen significant technological advances for photon radiation delivery in terms of precision by using IMRT, VMAT, and SBRT. These approaches can generate extremely conformal dose distributions including concave

isodose volumes that provide conformal target volume coverage and avoidance of specific sensitive normal structures [6, 7]. Further improvements in therapeutic ratio could be achieved by using particle beam RT, in particular proton and carbon ion therapy (see Chap. 11). This can lead to several advantages in terms of normal tissue sparing, better dose homogeneity, and a reduced dose bath effect (low radiation dose to normal tissue). However, both modern photon- and hadron-based treatments have been shown to be effective and are characterized by a favorable toxicity profile [8]. Dosimetric and/or clinical comparison studies between photon and hadron therapy for SGTs are very scant [8, 9]. Besides, due to the high cost of particle therapy and the very low number of equipped facilities, a careful selection of patients is absolutely critical.

In this chapter, we will focus on the role and the impact of photon RT for SGTs both in malignant and benign lesions. The majority of published retrospective papers includes heterogeneous series taking into account number of patients, histology, tumor sites (major vs minor salivary glands), stages, and RT settings (i.e., definitive, postoperative, or reirradiation); for this reason we have dedicated different paragraphs to detail curative RT treatment based on the following histopathologies: ACC, non-ACC high-grade, non-ACC low-grade, and non-malignant neoplasms.

11.2 Adenoid Cystic Carcinoma (ACC)

11.2.1 Indications and Role of Postoperative Radiotherapy (PORT)

The "gold-standard" treatment for potentially resectable ACCs consists in radical surgery providing free margins followed by PORT, although the role of RT has been debatable in the absence of randomized trials or prospective studies. The addition of RT with surgery has been reported to improve local control (LC) rates compared with surgical resection alone in all ACC sites. Five- and 10-year LC rates for combined modality treatment were 88–95% and 84–91%, respectively [10–13]. Garden et al. studied 198 patients with ACC of the head and neck treated with surgery followed by radiation. They demonstrated LC rates of 95%, 86%, and 79% at 5, 10, and 15 years, respectively. Improved treatment outcome led the investigators to recommend PORT as the routine treatment approach for most patients with ACC. In addition, Mendenhall et al. also stated that the optimal treatment for these patients is surgery followed by adjuvant radiotherapy [11]. The omission of adjuvant radiation was found to be an independent predictor of local recurrence in the study by the University of California at San Francisco (UCSF), including 140 patients [14]. Furthermore, the experience of Memorial Sloan Kettering Cancer Center published in 2008 showed improved LC for patients treated with PORT and supported the routine use of combined treatment in ACC [15]. However, some authors do not find a statistically significant effect of PORT on LC [16, 17]; others postulated that PORT may delay rather than prevent recurrence instead [18, 19].

The effectiveness of RT has been questioned by some other studies because of its lack of advantage in overall survival (OS) for the high rate of distant metastases and a relatively high probability of long-term survival after salvage therapy [14, 16, 20].

A recent study from the SEER database on 3026 patients reported by Ellington et al. suggested that PORT confers no survival benefit [21]; this was also confirmed by Lloyd et al. [22]. Some papers with opposed conclusions have been published. A retrospective series by Shen, on 101 patients diagnosed with ACC arising from all head and neck sites, showed at multivariate analysis that the addition of RT was a favorite predictor for LC and survival rates [23].

Several authors have retrospectively studied clinical and pathological features, attempting to identify significant prognostic factors in the presence of which PORT was highly suggested, but these factors still remain controversial. Various adverse parameters such as advanced tumor lesions, positive surgical margins, perineural invasion, and major nerve involvement have been suggested as the indication for PORT in ACC [11, 12, 14, 15, 24, 25].

In a recent paper by Ali at al. [26], pathological T4 stage without PORT was an independent predictor of local failure. However, after adjusting for T stage, patients who do not get PORT were more likely to have local recurrence: they had a 13-fold increased risk of local failure compared to patients treated with PORT. Vikram et al. recommended that patients with high-grade tumors and/or high-stage tumors benefited from PORT [27]. Histological grade was also considered in the paper by da Cruz Perez et al. They affirmed that grade 3 ACC should be considered as a specific entity within the ACC group, due to its typical aggressive biological behavior and relatively poor outcome; therefore it is needed an improved adjuvant treatment [28].

As for perineural involvement (PNI), it is not currently clear if microscopic evidence of perineural invasion has true prognostic significance in ACC and also available data are conflicting. Nevertheless, when the nerve involved is above a certain size, or "named," a prognostic factor can be established [29].

It is known that PNI occurs via contiguous spread along perineural spaces or within the nerve itself, and it is a microscopic feature of malignancy often confined to the main tumor mass. The PNI, even microscopic, may be an indication for PORT. In fact, it is sometimes associated with skip lesions along the nerve that significantly increase the risk of recurrence after resection even if negative margins are obtained [29]; besides, Chen et al. at the UCSF found that PNI was associated with local recurrence in patients treated with surgery alone but not in those who received postoperative radiation [14]. The authors regarded PNI invasion as a marker for subclinical extension of disease that may not be adequately addressed by surgery alone, even in the setting of an apparently complete surgical resection [14]. Besides, there is an association between PNI and margin status. In a paper by Khan, 15 out of 20 patients with positive margins displayed PNI as well, while only 5 of 17 with negative margins showed nerve invasion ($P = 0.02$) [20].

Bone invasion from ACC can be identified in advanced tumor arising from sublingual and submandibular gland, paranasal sinuses, nasopharynx, and lacrimal gland. Thompson et al. stated that an increased incidence of either recurrence or dying with disease in patients with both skull base involvement and bone invasion

suggests an adjuvant treatment [30]. Williams et al. found radiologically and histologically documented bony invasion of the lacrimal gland fossa by ACC very high, up to 76%. In this case, PORT could be hardly recommended, due to its poorly prognostic role [31].

Some reports have been shown that nodal involvement, with or without extracapsular extension (ECE), is independently associated with decreased overall and cause-specific survival, probably because it is a risk factor for subsequent distant metastasis [32]. The role of adjuvant RT after therapeutic neck dissection has been highly debated. Generally, patients treated with surgery and adjuvant RT showed comparable outcome with those treated by surgery alone [33]. Furthermore, regional recurrences are not usually identified in clinically positive node patients who undergo therapeutic neck dissection, whether or not adjuvant RT is administered [34].

The overall rate, from 15% to 44%, of occult neck metastasis for all ACC head and neck sites seems to be higher in oral cavity and oropharynx (22–31%) than those in the sinonasal tract (17%) or in the major glands (11–23%) [32–35]. Level II was the most frequently involved, with a reported incidence of 59.6%. Level III and IV regions were affected only in 22.5% of cases [32]. Besides, Lee et al. noted that the primary tumor site and peri-tumoral lymphovascular invasion were significantly associated with cervical lymph node metastasis [35]. On this basis, selective neck dissection should be considered for tumors of those sites showing lymphovascular invasion, in high-risk oral and oropharyngeal ACC [23, 32].

Lee et al. observed that regional recurrence was not identified in cN+ patients who underwent therapeutic neck dissection or in cN0 patients who had elective neck treatment, whereas regional recurrence was identified in four patients staged cN0 who did not have elective treatment of the neck [34, 35]. Although there was no significant difference in distant metastases or survival rates when END was performed in N0 necks, END could remove occult regional disease and provide patients with a regional recurrence-free life [34, 35]. However, elective neck irradiation (ENI) remains controversial. Balamucki et al. employed ENI in 64 out of 101 patients with undissected cN0; the remaining 37 were observed. Multivariate analysis of neck control revealed that ENI significantly influenced rates of neck control at 5 and 10 years [10]. On this basis, the authors advised to electively treat the first echelon nodes, particularly in patients with primary tumors at sites that are rich in lymphatics. However, contrary results have been published. Chen et al. [36] compared outcomes in a group of patients receiving neck irradiation and another group submitted to observation. There were no relapses in either group. In accordance with these results, their current policy is not recommending elective neck irradiation routinely.

Overall, PORT is suggested in all patients or at least in the presence of various adverse parameters such as advanced tumor stages (e.g., T3–4), positive or close surgical margins, PNI, and bone involvement [37]. Patients with T1/T2 tumors, negative margins, and negative neck disease did not have any benefit [38]. Radiotherapy treatment of the neck should be made on a case-by-case basis. However, ENI could be considered for tumors of those sites showing lymphovascular invasion and in high-risk oral and oropharyngeal ACC, when END is not performed [34, 35].

11.2.2 Definitive Radiotherapy

RT alone can be given to a subset of patients with early-stage resectable cancers depending on the location of the tumor, patients' wishes, and philosophy of the attending physician [10].

Patients with unresectable ACCs or gross residual diseases receiving conventional RT alone showed the poorest results in terms of LC ranging from 10% to 48% [27, 39, 40]. ACCs from paranasal sinuses can receive advanced photon beam techniques (IMRT and VMAT) allowing for a higher therapeutic ratio when a complete surgery cannot be performed because of invasion of the dura, brain, orbit, or nasopharynx. Spratt DE et al. stated that IMRT techniques with doses ≥70 Gy are a reasonable alternative to neutron radiotherapy in patients who present unresectable SGTs showing comparable disease control with fewer late complications [41]. Today, a more state-of-the-art radiotherapeutic approach is applied: instead of photon external beam treatment, a proton- or carbon ion-based irradiation is currently used. Exclusive modern particle therapy is not the object of the present chapter, but we want just to make a brief reference to mixed beam RT, based on photon and heavy particle. Pommier et al. studied 23 patients with nonmetastatic ACCs with skull base extension treated with both proton and photon RT to a total dose of 75.9 cobalt-Gy equivalent. The DFS and OS rates at 5 years were 56% and 77%, respectively [42]. Huber et al. compared RT with neutrons, photons, and a photon/neutron mixed beam in 75 patients with locally advanced, recurrent, or incompletely resected disease. They found the 5-year LC rate to be 75% for neutrons and 32% for the other two groups [43].

The advantage of neutrons over photons has also been shown in a prospective phase III trial conducted by RTOG and MRC [44]. However, the study was prematurely interrupted, but data from the 32 enrolled patients showed a 10-year LC of 56% in the neutron arm vs 17% in the photon arm. Long-term, treatment-related severe morbidity was greater in the neutron arm even if there was no significant difference in "life-threatening" complications. Neutrons were responsible for the increase in LC and toxicity [44].

More recently, carbon ion RT has been used in ACC, in the attempt to reproduce the high LC of neutron therapy without its toxicity. In the Heidelberg experience, a phase II trial (COSMIC) was designed to investigate the effects of dose escalation in the established mixed-beam regimen (photons+ carbon ions) with a total biologically effective dose of 80 Gy [45]. This study included patients with either inoperable disease or R2 or R1 resection (N = 53 patients), and most of them had ACC (89%). Three-year LC was 82%, and there was no significant difference between R1, R2, and inoperable patients. In the COSMIC trial, there were two patients with late osteoradionecrosis and one case of late internal carotid aneurysm [45].

Main characteristics and relative reported outcomes of ACC selected studies are reported in Table 11.1.

Table 11.1 Main characteristics and relative reported outcomes of ACC studies included in this chapter

Author	Observation period	No. of patients	Site	Histology	Type of treatment (pts)	RT technique (pts)	Dose/fractionation	Local control	Overall survival
van Weert et al. [13]	1979–2009	105	All sites	ACC	Surgery alone (6) PORT (81) RT alone (13) Not treated (5)	n.s.	50 Gy (2 Gy/fr) + 10–20 Gy (2–2.5 Gy/fr)	58% at 10 years	52% at 10 years
Balamucki et al. [10]	1966–2008	120	All sites	ACC	RT alone (44) PORT (76)	n.s.	72.4 Gy (range 60–79.2) 69.6 Gy (range 10.5–75.6) Conventional fractionation, hyperfractionation, or concomitant-boost	36% at 10 years 84% at 10 years	37% at 10 years 57% at 10 years
Gomez et al. [15]	1990–2004	59	All sites	ACC	PORT (54) RT alone (5)	IMRT (17) 3D-CRT (15) Conventional (27)	63 Gy (range 52.2–70.2)	81% at 10 years	65% at 10 years
Chen et al. [46]	1960–2004	140	All sites	ACC	Surgery alone (50) PORT (90)	Wedged pairs (21) Mixed beams (24) 2-field (11) 3-field (12) IMRT (22)	64 Gy (range 54–71)	77% at 10 years (61% surgery alone—84% PORT)	64% at 5 years
Mendenhall et al. [11]	1966–2001	101	All sites	ACC	RT alone (42) PORT (59)	n.s.	72.4 Gy (range 61.3–79.2) 67.8 Gy (range 10.5–76.8) Conventional fractionation or hyperfractionation	69% at 10 years (43% RT alone—91% PORT)	49% at 10 years (42% RT alone—55% PORT)

(continued)

Table 11.1 (continued)

Author	Observation period	No. of patients	Site	Histology	Type of treatment (pts)	RT technique (pts)	Dose/fractionation	Local control	Overall survival
Silverman et al. [25]	1971–2001	75	All sites	ACC	Surgery alone (25) PORT (50)	n.s.	59.8 Gy (range 45–72) Conventional fractionation	79% at 10 years 71.6% at 10 years	67.9% at 10 years 60.5% at 10 years
Khan et al. [20]	1955–1999	68	All sites	ACC	Surgery alone (18) RT alone ± chemo (8) PORT (41)	n.s.	57.3 Gy (mean dose)	n.s.	44% at 10 years
Garden et al. [12]	1962–1991	198	All sites	ACC	PORT	Single-appositional (75) Parallel-opposed (52) Wedged pairs (29) 3-field (40)	60 Gy (range 50–69) Conventional fractionation	86% at 10 years	65% at 10 years

ACC adenoid cystic carcinoma, *RT* radiotherapy, *PORT* postoperative radiotherapy, *IMRT* intensity-modulated radiotherapy, *3D-CRT* three-dimensional conformal radiation therapy, *n.s.* not specified

11.2.3 Target Volumes, Doses, and Technique

Target volume delineation is based on preoperative imaging, preoperative physical exam, operative findings, and pathological findings. It is strongly recommended to map preoperative macroscopic disease onto the PORT planning CT scan using image registration with pre-surgical CT, and in general two target volumes can be defined. A high-risk target volume is commonly determined if microscopically affected margins are found. An intermediate-risk volume generally encompasses anatomical sites at risk of residual disease in addition to the original areas involved and the operative bed. These two RT volumes are usually planned to receive a total dose of 66–70 Gy and 54–63 Gy, respectively, with conventional fractionation [37, 47]. Garden et al. detected a trend toward improved LC with doses >56 Gy and suggested a minimum of 60 Gy to the original tumor volume and 66 Gy when multiple margins are positive or there is extensive soft tissue involvement [12]. Harrison et al. found a reduced 10-year LC rate of 53% in patients treated with lower doses compared to 72% in patients treated with more than 57.5 Gy [48]. Simpson et al. showed a statistically significant improvement in LC for patients receiving doses >60 Gy [49]. In the study by Chen et al., RT doses lower than 60 Gy were an independent predictor of local recurrence [14]. The extension of postoperative intermediate-risk volume varies according to primary site and occurrence of PNI. It is still doubtful whether an "elective perineural volume" (i.e., a prophylactic volume in the shape of nerves) should be drawn or not in case of microscopic PNI. Contouring can be performed according to indications reported in 1008 Radiation Therapy Oncology Group (RTOG) phase II trial [47]. In case of superficial parotidectomy, superficial lobe tumors should always encompass the deep lobe (to depth of styloid process). For deep lobe tumors or with a complete parotidectomy, this volume must also cover parapharyngeal space and temporal fossa. Finally, it should be delineated from the skull base up to the stylomastoid foramen if the VII nerve (facial nerve) is not grossly involved. When the facial nerve is hardly implicated, the contour should include the facial nerve canal through the petrous temporal bone [47]. If the tumor grossly involves one of the named large nerves in that area, such as the lingual nerve (branch of V3), the inferior alveolar nerve (branch of V3), or the hypoglossal nerve (cranial nerve XII), then the skull base needs to be included in this volume. In particular, it has to be up to the hypoglossal canal for hypoglossal nerve involvement or foramen ovale for V3 branch involvement. Moreover, if the inferior alveolar nerve (branch of V3) is involved near the skull base, intermediate-risk volume should include Meckel's cave [47]. When only focal perineural invasion is pathologically found, it can be questionable if it routinely includes nerve pathways to the base of the skull in treatment portals. For ACC of the palate or paranasal sinuses, the base of the skull is usually included because of its proximity to the tumor bed.

Contouring guidelines are available to guide radiation oncologists in the delineation of cranial nerve anatomy [50, 51].

In case of ACC involving sites with a rich lymphatic drainage or showing lymphovascular invasion, the neck has to be treated. If neck surgery has not been performed, ENI must be considered, and it should include at least the first echelon nodes. This low-risk volume usually receives 45–54 Gy.

The resultant target volumes are complex three-dimensional shapes, in particular for ACC arising from minor salivary gland of paranasal sinuses. Besides, several sensitive anatomical structures as the globes, lacrimal glands, optic nerves, chiasm, brainstem, and brain lie immediately adjacent or in close proximity to target volumes. Conventional RT has been associated either with incomplete target coverage or severe toxicity (e.g., radiation-induced blindness, retinopathy and neuropathy, dry syndrome) [19]. IMRT and VMAT, allowing steep dose gradients close to the target, turned out to be effective methods to optimize treatment planning of ACC and to deliver higher doses to the targets while minimizing the doses to the organs at risk [52–55]. Furthermore, the IMRT technique allows the simultaneous delivery of different dose levels to different target volumes within a single treatment fraction by using the "simultaneous integrated boost technique" or "SIB-IMRT" [56].

Target volume definition and RT dose distribution with postoperative VMAT in a case of ACC of submandibular gland are shown in Fig. 11.1.

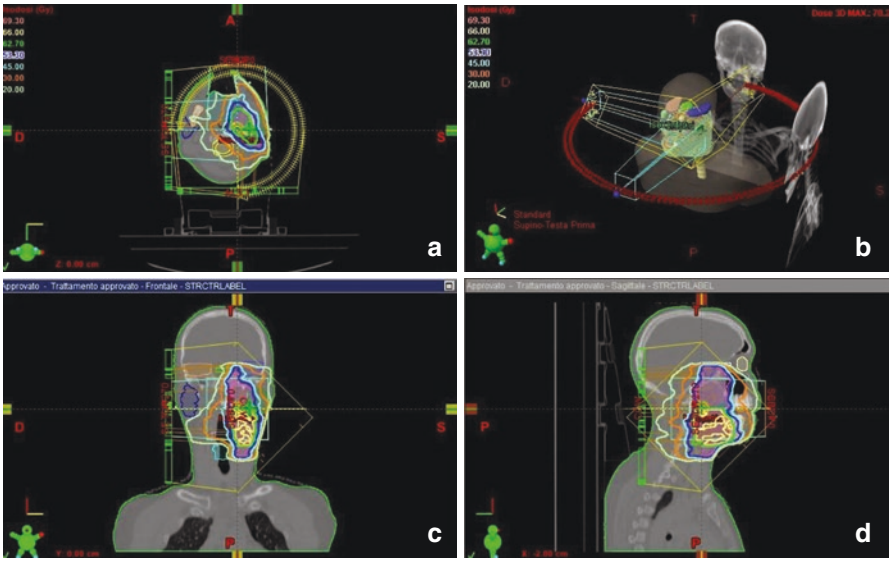

Fig. 11.1 ACC of the left submandibular gland (stage pT2R1, PNI, N0): treatment planning for postoperative VMAT 66 Gy. Figures (**a**, **c**, **d**) show axial, coronal, and sagittal, respectively, computed tomography (CT) simulation images. High-risk planning target volume (PTV) (66 Gy), in red, includes the surgical bed with wide margin along cranial direction due to the presence of R1; low-risk PTV (56.1 Gy) includes HR-PTV with margin and skull base up to the emergency of V cranial nerve. A three-dimensional view of VMAT plan with arches is reported in (**b**)

In the definitive non-operative setting, i.e., unresectable or inoperable cases, treatment volumes follow similar principles, but the total dose is usually carried to 70 Gy in 35 fractions to macroscopic disease, i.e., the high-risk volume [41, 57].

11.3 High-Grade Non-adenoid Cystic Carcinoma (Non-ACC)

11.3.1 Indications and Role of Postoperative Radiotherapy

Surgery is the preferred up-front treatment for high-grade non-ACC. The aim of surgery is complete excision of the tumor along with adequate margins, and incomplete gross tumor resection (R2) should be always avoided.

Whether radiotherapy should be considered for *all* as opposed to *selected* patients after resection is debated. Even if the (beneficial) role of PORT is supported only from retrospective studies, almost all studies consistently show an advantage mostly in terms of locoregional control (LRC) by adding PORT to surgery [38, 57–61]. One area of debate is represented by completely resected (R0) stage I (–II) disease without other risk factors, where some authors recommend observation rather than postoperative RT. For major SGTs, stage I would include T1N0 lesions or those confined to the parenchymal gland up to 2 cm in greatest dimension. In the matched pair analysis from Memorial Sloan Kettering Cancer Center, no benefit was found for PORT in stage I–II disease after complete resection [38]. In the Dutch series, completely resected T1–T2 lesions showed a 95% long-term control rate [57]. However, most authors would still support the adjunct of RT after R0 surgery for *all* high-grade lesions regardless of the stage.

There is little doubt that PORT is indicated for patients with extraglandular extension (T3–T4 tumors), incomplete or close resection, bone invasion, perineural invasion, and pathologically involved lymph nodes (pN+) [57].

Another issue is whether a "planned" R1 resection (a resection that ends up in microscopically positive margins) is acceptable under specific circumstances or surgery should always aim at achieving negative margins. This may happen when the tumor is close to the facial nerve, and thus complete resection with a margin would imply the sacrifice of the nerve. According to the experience of Shah et al. [62] at a median follow-up of 5 years, only 2 local failures were observed in a series of 50 parotid cancers operated mostly (82%) to close or positive margins and irradiated afterward up to 60 Gy. While the authors conclude that "facial nerve-sparing surgery" followed by RT (60 Gy) results in good LRC rates, it should be noted that only 20% of the patients in their series had high-grade tumors. Moreover, another 20% of local failures are to be expected with a longer follow-up [63]. PORT improves LC over surgery alone after R1 resection, but R1 resection remains a poor predictor of LC despite PORT [64]. Therefore, both the risk and amount of R1 resection should be minimized. Regarding facial nerve, if it is directly infiltrated and not functional, it should be sacrificed. However, if the nerve is functioning and not directly infiltrated, most authors would agree that conservative surgery ("tumor peel off") followed by PORT to 60–66 Gy is an acceptable strategy even if it may be associated with a slight increase in the risk of local failure.

Basically, all high-grade non-ACC are associated with a high risk of occult nodal spread. Squamous cell carcinoma, undifferentiated carcinoma, adenocarcinoma, and high-grade MEC have a remarkable (>30%) risk of occult nodal spread [59]. Besides pathology, another predictor of nodal spread is primary tumor stage [36, 65–68], while tumor location is somewhat controversial [57, 63]. Parotid tumors with facial paralysis are associated with a high percentage of occult lymph node metastases as well [69, 70]. ENI is highly effective to prevent regional failure [36]: 10-year regional control rates in cN0 patients treated without and with ENI between 1960 and 2004 at UCSF were 74% and 100%, respectively, $p = 0.0001$. Therefore, ENI is a reasonable alternative to neck dissection. The choice between ENI and surgery is related to the overall treatment strategy (including the treatment of the primary disease) and the benefits (if any) of surgical staging. One may argue that in case of a small (cT1N0) major SGT, a complete resection of the primary to negative margins (pT1, R0) along with pathological confirmation of negative lymph nodes (pN0) may lead to withhold PORT. In another scenario of a larger primary high-grade non-ACC for which the indication to PORT can be anticipated, the elective surgical treatment of the neck may be withheld provided that the neck is properly imaged and staged.

As previously mentioned, data on the outcome of high-grade non-ACC after combined therapy come from retrospective studies. Unfortunately, such retrospective series often include low-grade tumors and/or ACC as well. For instance, in the Dutch Head and Neck Oncology Cooperative Group report on 498 patients treated with surgery with ($N = 386$) or without ($N = 112$) PORT between 1984 and 1995, it is impossible to tease out the amount/percentage of patients with high- versus low-grade tumors (and thus their respective outcome) [57]. Anyhow, at a mean follow-up of 76 months, actuarial 5-year LC rate is 84% for surgery alone and 94% for combined surgery and RT ($p < 0.0005$). Independent prognostic factors for LC were treatment, with a relative risk for surgery alone compared with combined treatment, clinical tumor size, tumor location, status of the resection margins, and bone invasion [57]. A very similar outcome (5-year LRC: 89%) was reported in a subsequent group of patients treated for parotid carcinoma in Rotterdam between 1995 and 2010 [71]. Interestingly, in this series, more locoregional failures were reported in patients with squamous cell and high-grade MEC (21% and 19%, respectively) than in patients with other histological types ($p = 0.04$) and more distant metastases in patients with ACC and adenocarcinoma (20% and 19%, respectively) than in patients with other types ($p = 0.03$). Finally, in this analysis, more distant than locoregional failures were observed [71]. It should be noted that while most of failures occur within 5 years from initial surgery, another ≈10% and ≈20% of patients develop disease recurrence at 10 and 15 years, respectively, mostly at distant sites [36].

In the experience of the Danish Head and Neck Cancer Group (DAHANCA), out of 871 patients diagnosed with SGT between 1990 and 2005, 425 patients (49%) received a combination surgery and RT, while 350 (40%) were treated with surgery alone. Indications for PORT were incomplete tumor resection, perineural extension, high disease stages, lymph nodes with extracapsular spread, and high-grade tumors.

High-risk pathology included ACC, SCC, carcinoma ex pleomorphic adenoma, G2/3 adenocarcinoma, and G3 MEC. Another major difference to current standards is that the neck was rarely addressed electively. At a median follow-up of 78 months, 334 patients (38%) experienced recurrence. Interestingly, 23% of patients developed locoregional recurrence only (15% primary, 3% nodal, and 5% both), while 8% had also distant metastases and 8% developed only distant disease. In multivariable analysis, stage III/IV, lymphovascular invasion, involved or close microscopic margins, and high-risk pathology were all prognostic factors for both recurrence-free and overall survival. Unfortunately, the treatment approach (surgery vs combined surgery and radiotherapy) was not tested in the model [72].

In the recently published experience by the Princess Margaret Hospital, carcinomas of the major salivary glands treated with surgery and PORT between 2000 and 2012 were analyzed. High-risk pathology was defined, on central review, according to both histologic grade and WHO histologic subtype criteria, and included ACC, salivary duct carcinoma, squamous cell carcinoma, G2/3 adenocarcinoma, G2/3 MEC, G2/3 carcinoma ex pleomorphic adenoma, carcinosarcoma, undifferentiated (small-cell, large-cell, or lymphoepithelial) carcinoma, and G3 of other histologic subtypes. Out of a total of 304 eligible patients, 190 (62.5%) had high-risk pathology, including 55 patients with ACC. About 60% of the patients were treated with IMRT and the remaining ones with 3D CRT. At a median follow-up of 82 months, the estimated 5-(10-)year LC, RC, and DC were 96% (96%), 95% (94%), and 80% (77%), respectively. Only 13 patients developed local failure (LF); among these cases, 11 (85%) had positive resection margins ($p = 0.02$), and 10 (77%) had lymphovascular invasion ($p = 0.01$). During follow-up, diagnosis of DM was the most frequently observed treatment failure ($n = 62$) with a median DM-free interval of 21 months (range, 5–141); 74% (46/62) DM failures were with isolated DM [73].

Few studies focused on selected pathology types only. Resected MEC of the parotid gland treated with adjuvant radiotherapy for high-risk features was the topic of the paper of Chen et al. [74]. At multivariable analysis on 61 patients, high tumor grade (hazard ratio = 7.92) and T4 disease (HR = 3.35) were found to be independent predictors of decreased survival, with the former also predicting for distant metastasis and the latter predicting for local-regional recurrence. At a median follow-up of 45 months, the 5-year estimate of overall survival was 83% for patients with non-high-grade tumors, compared to 52% for those with high-grade histology ($p = 0.001$). In a similar paper by MDACC on 145 patients with MEC of the salivary glands treated primarily with surgery and (60%) PORT, grade and stage confirmed to be the major determinants of overall survival [75]. Patients with T3–4 and high-grade disease had a only 10% chance of long-term survival [75].

A couple of papers focused on carcinoma ex pleomorphic adenoma (CXPA) of the parotid gland that is a relatively rare malignancy that, as implied by its name, is believed to evolve from a preexisting benign adenoma [76]. In the first one [77], the authors retrospectively compared the outcome of high-grade tumors of the parotid gland (21 CPXA and 52 non-CXPA). Despite having similar stage of cancer and extent of surgical resection, patients with CXPA had a lower disease-specific survival compared to non-CXPA high-grade primary parotid cancer ($p = 0.02$). CXPA

of the parotid gland seems a more aggressive cancer compared to non-CXPA high-grade primary parotid cancer. In the second one [76], 63 patients were treated with definitive surgery for carcinoma CXPA of the parotid gland, of whom 40 patients (63%) received also PORT to a median dose of 60 Gy (range, 45–71 Gy). Adenocarcinoma (29 patients), salivary duct carcinoma (16 patients), and ACC (9 patients) were the most common malignant subtypes. At a median follow-up of 50 months (range, 2–96 months), the use of PORT significantly improved 5-year LC from 49% to 75% ($p = 0.005$). At multivariate analysis, pathologic involvement of cervical lymph nodes was the only independent predictor of overall survival. In conclusion, surgery followed by PORT should be considered the standard of care for patients with carcinoma CXPA, which is an aggressive neoplasm.

11.3.2 Definitive RT

High-grade non-ACC includes a heterogeneous group of primary tumors that share the feature of being considered not particularly sensitive to ionizing radiations. Therefore, definitive RT is not considered an alternative to up-front resections and is usually reserved for unresectable lesions, for inoperable patients, and for those who refuse surgery. Definitive radiotherapy with photons has been associated in the past with dismal results. Two-dimensional photon-based RT was the control arm of a RTOG-MRC randomized study testing neutron therapy in inoperable or unresectable malignant SGTs [78]. The study was discontinued after enrollment of only 32 patients of which 25 were evaluable. Patients had remarkable advanced disease; median primary tumor size was 6 cm (range, 3–16 cm), and 1/3 of patients had clinically positive nodes. Moreover, pathology was not stratified by arms. As expected, at 10 years, the LRC in the control photon arm was only 17% [78]. Long-term LRC rates around 25% have been reported by others [79, 80].

In other series, 5-year LRC rates with photons have been reported around 50% [46, 57, 81], perhaps due to the higher dose of RT delivered (66–70 Gy). At UCSF, 45 patients with newly diagnosed SGTs were treated with definitive radiation to a median dose of 66 Gy (range, 57–74 Gy) between 1960 and 2004. Indications for primary radiation treatment were as follows: 17 surgically unresectable (38%), 13 with gross residual disease after subtotal resection or open biopsy (29%), 12 medically inoperable (27%), and 3 refusal of surgery (7%). The median tumor size, as determined by physical examination or radiographic imaging (or both), measured 3.4 cm (range, 1.2–9.2 cm) with six patients having tumors in excess of 7 cm. None of the patients had clinical or pathologic evidence of regional lymph node disease at the time of presentation, and only two patients received chemotherapy in addition to RT. The series includes both low- and high-grade SGTs. At a median follow-up of 101 months (range, 3–285 months), the 5-year and 10-year rate estimates of LC were 70% and 57%, respectively. A Cox proportional hazard model identified T3–4 disease ($p = 0.004$) and radiation dose lower than 66 Gy ($p < 0.001$) as independent predictors of local recurrence [46].

Results of contemporary photon-based series employing modern techniques (3D-CRT, IMRT, SBRT) are even better. From 1990 to 2009, 27 patients with unresectable SGC (63%, with HG tumors) underwent definitive photon radiotherapy at MSKCC. Nodal involvement was found in nine patients. Median primary tumor size was 5 cm (range, 3–12 cm). Median dose of radiotherapy was 70 Gy, with 9 patients receiving IMRT and 18 3D-CRT. Chemotherapy was given to 18 patients, most being platinum-based regimens. With a median follow-up of 52.4 months, the 5-year actuarial LC was 55% (±24.2%). High grade was significant for an increased rate of DM (intermediate grade vs low grade, $p = 0.04$, HR 7.93; high grade vs low grade, $p = 0.01$, HR 13.50) [82]. Karam et al. have reported encouraging results on a selected group of patients treated with hypofractionated SBRT boost [83].

In conclusion, surgery remains the treatment of choice for patients with HG non-ACC. For patients who have unresectable disease, are inoperable, or simply refuse surgery, definitive radiotherapy may offer a chance of cure. In this setting, heavy particles are usually preferred, but in their absence, photon-based IMRT may be a reasonable option as well.

11.3.3 Target Volumes, Doses, and Technique

In the postoperative setting, the tumor and involved lymph node bed constitute the target volume at intermediate risk. Electively treated uninvolved nodal regions represent the target volume at lower risk. Within a simultaneous integrated boost plan in 30 fractions, the former is usually planned to receive 60 Gy while the latter 54–56 Gy [73].

Regarding the intermediate-risk volume, preoperative imaging and examination findings, operative notes, and pathology findings should guide contouring to ensure that all areas originally involved by disease are targeted. For patients with partial removal of the involved gland (i.e., superficial parotidectomy), the whole remaining gland (i.e., the deep lobe of the gland) is part of the intermediate-risk target volume.

Another area of possible concern is the skull base, in the presence of "named" nerve perineural invasion, though this is more common for ACCs.

Regarding the nodal stations at risk of subclinical disease (low-risk volume), ipsilateral cervical lymph nodes are routinely targeted either with surgery or RT as previously discussed. Elective nodal irradiation to a dose of 54 Gy (in 30 fractions) is usually reserved for patients without clinical or pathologic lymph node involvement, while the areas originally involved and those with extracapsular extension are planned to receive 60 Gy and 64–66 Gy, respectively, in 30 fractions. The nodal regions to target depend on the location of the primary tumor and the nodal levels macroscopically involved. Periparotid and ipsilateral lymph nodes (level II) are most frequently involved in the tumors of parotid gland, although skip metastases to level III have been observed. In one study, for patients with three or fewer positive nodes at neck dissection, level IV and level V were positive in less than 10% of the

cases [36, 59]. Therefore, in elective treatment of the neck, at least levels I, II, and III should be included [36, 65], while levels IV and V can be omitted in the cN0 neck. Level Ib nodes should be included when level II is involved, and levels IV and V nodes should be targeted when levels II and III are involved [36]. Submandibular gland cancers typically spread to levels I–III. Minor salivary gland cancers in the head and neck region can often be midline and may necessitate bilateral lymph node irradiation. Treatment of the contralateral neck should also be considered for patients who have multiple ipsilateral lymph nodes involved. In one recent paper on patients with resected major SGTs treated with PORT, regional failure occurred in 3 (2%) out of 171 patients treated with IMRT; interestingly, all patients failed outside the low-risk volume: ipsilateral level VI b ($N = 1$), ipsilateral level V ($N = 1$), and contralateral level V ($N = 1$) [73]. Other studies suggest that elective treatment of the neck is at least as effective as surgery in controlling subclinical disease [36].

Sometimes a third volume at higher risk is identified (CTC high risk). The Dutch study supports a higher than 60 Gy volume for incompletely resected regions [57]. This volume typically receives an additional boost of 6–10 Gy to areas considered at higher risk of microscopic/R1 disease, such as those corresponding to positive margins and extracapsular tumor extension. The boost is usually achieved by a simultaneous integrated boost to the nominal dose of 64–66 Gy in 30 fractions.

Treatment should start as soon as possible after surgery and possibly not longer than 6–8 weeks from surgery, though clinical evidence is controversial [57, 84].

Target volume definition and RT dose distribution with postoperative VMAT in a case of high-grade MEC of the parotid gland are shown in Fig. 11.2.

In the definitive non-operative setting, treatment volumes follow similar principles, but the total dose is usually carried to 70 Gy in 35 fractions to the gross tumor volume [57]. Wang et al. reported LC as high as 85% with accelerated hyperfractionated photon therapy. The follow-up was rather short, and the results have not been updated [85]. Regarding the technique, IMRT may help to limit both acute and late toxicity rates [86] besides the possibility to paint the dose to the various targets.

11.4 Toxicity

Radiation-induced side effects are the same observed in head and neck district. They can be acute (i.e., mucositis, xerostomia, loss of taste, dysphagia) or late (i.e., osteoradionecrosis, neck fibrosis, trismus), these latter in particular when cancer arises from major salivary gland. Previous surgery limits the amount of radiation dose prescribed and may increase the risk of late toxicity.

Garden et al. [84] reported complications of irradiation in 51 out of 160 patients receiving PORT for minor SGTs. The most relevant were decreased hearing, radiation-induced injury to the visual pathway, and bone necrosis or exposure. However, these complications have been hardly ever seen during the last decades with improved radiation therapy techniques [84].

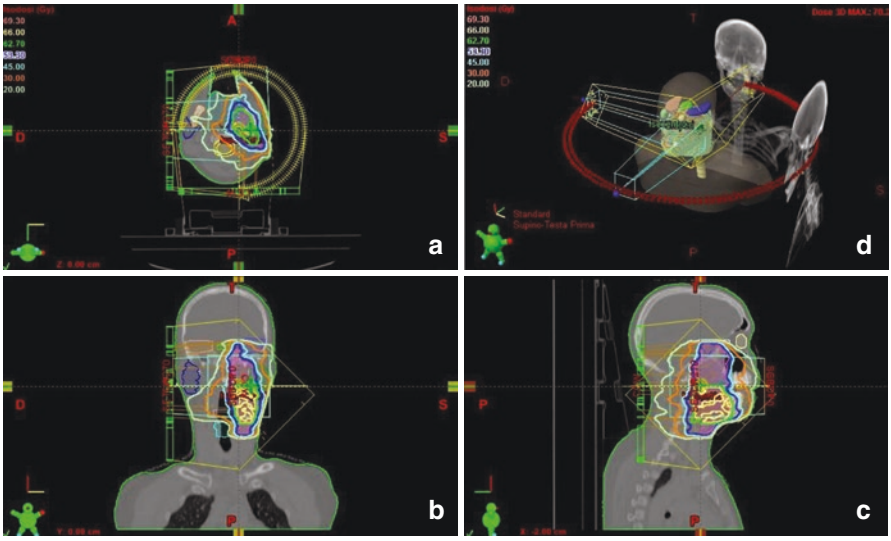

Fig. 11.2 High-grade MEC of the left parotid gland, stage pT4a R1 (multiple surgical positive margins), PNI, and N2b. This is a treatment plan for a postoperative RT VMAT dose 70 Gy. Pictures show axial (**a**), coronal (**b**), and sagittal (**c**) computed tomography simulation images. High-risk planning target volume (PTV) (70 Gy), in red, includes the surgical bed with wide margin along cranial direction due to the presence of R1; intermediate-risk PTV (60 Gy) includes HR-PTV all ipsilateral neck and skull base up to the emergency of VII cranial nerve; low-risk PTV (54 Gy) includes HR-PTV, IR-PTV, and the right neck. Figure (**d**) shows a three-dimensional view of PTVs and neurological organs at risk (OARS) eye (light green), left eye (yellow); left optic nerve (white) optic chiasm (lilac); brainstem (green)

In a series of patients treated after 2000 with either postoperative 3D-CRT or IMRT after a median follow-up of 82 months, the 5- and 10-year cumulative incidence of RTOG grade 3 late toxicity was both 3%. No grade 4 or 5 was reported [73]. In another study, the cumulative incidence of grade 2 toxicity at 5 years after surgery and PORT was 8% [71]. Concomitant chemotherapy may enhance the intensity of side effects. Therefore, nowadays, most of the patients develop minimal effects.

11.5 Reirradiation

There are no randomized trials or prospective studies specifically on reirradiation of SGTs. It can be assumed that most of the general considerations and recommendations may apply to recurrent SGTs. Retreatment usually involves additional surgery, if feasible, and PORT. In certain histological subtypes (e.g., ACC), retreatment of locally recurrent disease yields prolonged survival [49]. Reirradiation must always be considered for local recurrences not amenable to surgical therapy, and in ACC reirradiation should be taken into account even in the presence of distant metastasis.

Several photon techniques, such as IMRT, stereotactic RT, CyberKnife, and Gamma Knife radiosurgery, have been used with promising results in terms of acute and late toxicity [87–89]. Lee et al. reported on eight patients with skull base recurrences who underwent Gamma Knife radiosurgery. All patients experienced symptomatic response, usually pain resolution. The median local free from local progression and survival were 15.4 and 21.2 months, respectively [87]. In a paper by Karam, 18 patients diagnosed with recurrent, previously irradiated, SGTs were treated with SBRT reirradiation (CyberKnife) with a median dose of 30 Gy given in 5 fractions with a median cumulative dose of 91.1 Gy. The 2-year OS and LRC rates were 39% and 53%, respectively. However, long-term toxicity analysis revealed four patients in the reirradiated group with soft tissue necrosis, correlated with the cumulative dose [89].

11.6 Chemoradiotherapy (CRT)

There is no convincing evidence on the efficacy of CT in treating SGT patients with curative intent, both in postoperative and radical setting. Amini et al. retrospectively reviewed 2210 patients with resected major SGTs using data from the National Cancer Database. They found that OS was significantly inferior with adjuvant CRT ($n = 368$) compared with RT alone ($n = 1842$) ($p = 0.02$), and patients treated with multiagent chemotherapy appeared to have a worse OS, compared with single-agent chemotherapy ($P = 0.03$) [90]. In a paper by Mifsud, outcome of patients treated from 1998 to 2013 with postoperative CRT (37 patients) or RT (103 patients) was analyzed. A multivariate analysis showed a trend toward a benefit in PFS from CRT, but it was not statistically significant [91].

Therefore, the RTOG is conducting a phase II randomized trial (RTOG 1008) to explore the utility of a platinum-based adjuvant CRT in high-risk patients. High-risk factors are the following: histological types as salivary duct carcinoma, grade 2/3 MEC, grade 2/3 adenocarcinoma, grade 3 ACC, and grade 3 acinic cell carcinoma, pathologic stage III–IVB, and positive/close surgical margins [47]. Until the results of this trial will be available, the standard use of CRT for advanced SGTs is not recommended.

11.7 Low-Grade Non-adenoid Cystic Carcinoma (Non-ACC)

11.7.1 Radiotherapy: General Considerations

Low-grade (LG) SGTs are a constellation of different histologies [4]. While certain papers report on LGSGTs combining different histologic types, others are focused on specific subtypes (see the following sections).

Among the former, Walvekar et al. compared 34 patients with low-risk histology and grade, negative margins, and no ECE with 18 patients with low-risk histology and grade but with ECE and positive margins. Inclusion of ECE and margin status

substantially improved the prediction of disease recurrence, supporting PORT for low-risk histologies with positive margins or ECS [92]. Richter et al. reported on a small series of 17 T1–3 patients operated for low-/intermediate-grade MEC and acinic cell carcinomas of the parotid with only one negative factor, close (≤5 mm) or positive margins. They coded as patients with positive margin also the cases in which the tumor was "peeled" off the VII nerve [93]. The operative (parotid) bed was treated with a modest margin; the neck was included in a few cases (policy no longer followed). Sixteen patients were treated with a wedged-pair technique or three-dimensional conformal radiation therapy (3DRT) using 6 mV photons, and one patient received 6 mV photons and 20 MeV electrons using a mixed-beam approach. The range of doses to the parotid was 45–66 Gy, with a median dose of 63 Gy mostly with daily fractions of 1.8–2 Gy; no disease failures were reported and acute and late toxicity were minimal [93].

Recently, Jae-Keun et al. from Korea reviewed the outcome of 179 LGSGTs. Various histologies were included, mainly LG MEC, ACC without solid component (tubular or cribriform subtypes), acinic cell carcinoma, and LG adenocarcinoma [94]. During the study period, radiation techniques were mainly 3D-CRT ($N = 98$) and IMRT ($N = 27$), with a median dose of nearly 60 Gy (range 50–66) by 1.8 or 2.0 Gy per fraction over 5.5–6 weeks. Recurrence-free survival (RFS) was chosen as primary endpoint because there were only two disease-specific deaths in their series. Nodal status (N1–3 vs N0) had significant impact on RFS (univariate and multivariate analysis). RFS was worse for patients with pathological risk factors, lymphovascular invasion being the strongest determinant (it was significant at univariate analysis). Only the presence of cancer cells at the margin of resection and not close margins (<5 mm) was significantly detrimental to RFS both at univariate and multivariate analyses. Contrary to common beliefs, less than total resection was equivalent to total resection (provided resection margins were not positive) [94].

Finally, the addition of PORT was highly significant in multivariate analysis in terms of improved RFS. They compared patients with N0 and negative pathological risk factors with patients with positive node/pathological risk factors. Results were equivalent in the first group with or without PORT, while in high-risk group among 13 patients without PORT, 6 experienced recurrence (46.2%; $p = 0.001$) versus 6.8% of the irradiated patients [94].

In conclusion, they stated that advanced T stage, nodal status, and pathological risk factors (positive margins, PNI and lymphovascular invasion, extraparenchymal extension) are an indication to PORT [94].

Therefore, PORT may be indicated in a substantial proportion of LGSGTs: actually, in the Jae-Keun series, only 10% of the patients had positive node, but approximately 50% of the patients had pathological risk factors [94].

11.7.2 Radiotherapy for LG and Intermediate-Grade (IG) MEC

Several grading systems have been reported for salivary MEC: AFIP, Brandwein, and Healey grading systems, all include LG (low-grade), IG (intermediate-grade),

and HG (high-grade) MEC [95]. Not all authors report an IG group [96], but most studies have suggested that there is no statistically significant difference between patients with LG and IG MEC in OS or DFS [97–101].

The role of adjuvant radiation therapy for patients with MEC of the parotid gland is based on data from institution reviews and lacks data from randomized controlled trials.

However, in the Liu study, the LG tumors showed better survival outcomes compared to patients with IG tumors for whom a significantly worse outcome was found [102]. Furthermore, in the Mc Hugh series, IG MEC had more local, regional (nodal), and distant relapse vs LG MEC (8%, 4.4%, and 4.4% vs 0%) in spite of similar OS and DFS [99]. IG has more often aggressive features (such as positive or close surgical margins, perineural or lymphovascular invasion, and extraglandular extension) [98, 99]. This probably explains why, e.g., in the Chen study, PORT was applied in 25% of the LG cases, 37.2% of the IG, and 79.9% of the HG cases in MEC [101]. Finally, Ozawa et al. combined IG tumors with HG tumors in assessing OS and DFS [103].

The criteria for PORT in MEC (all grades) include multiple factors: patients with HG lesions, stage III/IV lesions, positive lymph node status, positive margins, incompletely excised tumors, perineural/lymphovascular invasion, extraglandular extension, and tumors of the deep lobe of the parotid [97, 99, 102]. Also the primary site (major vs minor salivary glands), age (>60 years), positive margins, tumor size (>2.5 cm), pattern of invasion (broad-pushing borders vs infiltrative permeation), and length of time that the tumor was present have been shown to be associated with prognosis in MEC [104].

Specific indications to PORT for LG/IG MEC can be found in few papers: 14 LG lesions had PORT in the series by Guzzo et al. due to microscopic residual and/or advanced stage [96] and 1 LG patient in another series because of close surgical margins [105]. Rapidis reported 6 cases with PORT; 3 out of 4 IG had positive margins [98]. In the largest available series of the 30 patients with LG tumors, 12 (41.4%) underwent PORT due to evidence of positive or close margins in 9 patients and PNI in 3 patients [99]. Advanced stage may represent an indication to PORT as well [99].

Finally, Olsen reported on two cases of LG MEC treated with PORT for positive surgical margins and PNI [106].

In summary, although evidences are weak, PORT may be considered in selected LG/IG patients that have a high risk of recurrence [99].

According to the update 2003 of the "Standards, Options, and Recommendations" (SOR) project, for completely resected patients, PORT should not be used in case of LG stage I and II tumors but should be used for LG stage III and IV tumors. For patients with incomplete macroscopic or microscopic residual disease, PORT must be delivered [107]. As for minor salivary glands, Vander Poorten [108] reported that most minor SGTs were treated with surgery and PORT, with the exception of completely resected LG, low-stage MEC, and well-resected PLGA [109]. Mean doses delivered in PORT range around 60 Gy in conventional fractionation ranging from 40 to 66 Gy [97, 98, 102, 105, 106]. According to Hosokawa, 5-year LC was worse

with a dose lower than 55 Gy for patients with positive margins; however, the fraction of LG/IG cases in this subset analysis was not available [97].

The treatment volume includes generally the operative bed alone. Elective ND should be avoided in LG or IG tumors [95]. Actually, cervical lymph node metastases from MEC have been reported in tumors of all sites and grades, although lymphatic spread is considered overall very rare event for LG MEC, with a range reported between 0% and 2.5% [104]. Chen et al. reported a percentage of 3.3% of positive nodes at the levels I–III for LG tumors and 8.1 % for IG. Involvement of levels IV–V was more uncommon (0.4–0.6%). All patients with LG and IG MEC with positive lymph nodes in levels IV to V also had positive lymph nodes in levels I to III [101].

11.7.3 Radiotherapy for Acinic Cell Carcinoma

Acinic cell carcinoma (AciCC) is an uncommon low-grade (LG) malignant epithelial salivary gland cancer. Patients with well and moderately differentiated disease exhibited 20-year survivals of 97.79% and 83.33%, respectively, but despite being a predominantly LG cancer, it may have an aggressive behavior developing nodal and distant metastases, even many years after the initial diagnosis and treatment [108].

AciCC more often arise in parotid glands. Other sites, such as sinonasal cavities, are definitely less frequent [110]. Primary site may have an influence on survival. Biron et al., who compared patients with parotid AciCC to a matched cohort of AciCC of sinonasal cavities, found a higher 10-year OS for parotid tumor in comparison with paranasal sinus lesions (100% vs 52.3%); DFS was also higher, although not significantly different [110].

Primary radiotherapy should be restricted to patients not suitable for surgery or refusing surgery because AciCC is considered not particularly radiosensitive [111].

PORT is not frequently used in AciCC. Spafford et al. in 1991 proposed a series of indications for PORT in AciCC: recurrent tumor; equivocal or positive margins, or evidence of tumor spillage; tumor adjacent to the facial nerve; deep lobe involvement; lymph node metastases; extra-parotid extension PNI; and large tumors (e.g., greater than 4 cm) [112–114]. A total of 1241 cases of parotid AciCC in the Surveillance, Epidemiology, and End Results (SEER) Program database from 1988 to 2007 were identified and analyzed by Andreoli et al. [115]. Comparison groups were surgery and surgery plus RT. When comparing surgery alone with surgery plus RT, there was no statistical difference in OS when stratifying for stage. Similarly, adjuvant RT did not demonstrate a survival advantage when stratified by histologic grade of tumor. The authors concluded that PORT does not confer a survival advantage in low-grade and early-stage tumors and that RT can be spared for these patients, although the highest-grade and highest-stage tumors were fewer in number in this series. The most important limitation of this study is the lack of recurrence data available in the SEER database, which precludes the analysis of disease-free survival or local disease control. Similarly, surgical margin status is a key variable often used to determine the need for PORT, but this information was unavailable for these patients [115].

In the small study by Liu, no difference in survival rate was observed between 29 patients with surgery alone and 8 patients treated with surgery and adjuvant radiation. Patients older than 60 years with a fixed mass, high-grade tumor and nodal stage, perineural invasion, and angiolymphatic invasion had adverse OS and DFS ($P < 0.05$) [114].

Biron et al. [116] identified 2061 patients with AciCC 1973–2009 in the SEER database, although clinical information were available for 614 patients. Eighty-seven percent were grade I or II. Patients who received surgery alone had the highest 20-year DSS (92.4%), followed by those treated with surgery and RT (71.9%) or RT alone (62.3%).

This difference between treatment modality could not be accounted for by differences in grade, stage, sex, subsites, or other factors correlated with survival.

These data are difficult to interpret given that the basis for the decision to give adjuvant radiation therapy is unknown (e.g., the presence of positive margins). Authors concluded that despite the limitations in interpreting these data, histologic grade is a stronger predictor of survival than TNM classification [116].

According to Vander Poorten et al., caution should be, however, exerted as the SEER analysis does not correct for involved resection margins or initially inadequate treatment, which accounts for a substantial part of AciCC patients. Even after a "rough" correction for stage and grade, significant selection and information bias is still likely present in the retrospective SEER data [117].

11.7.4 Radiotherapy for Polymorphous Low-Grade Adenocarcinoma (PLGA)

The role of PORT in PLGA has not been proven so far.

Evidence for PORT is considered weak [118] due to the rarity of this tumor and its long natural history (requiring a long follow-up to establish the recurrence potential).

No relapse was reported in the review of Uemaetomari et al. [119] in cases of negative surgical margins. However, wide resections with clear margins of the parotid gland might be difficult to obtain without the sacrifice of the facial nerve in certain cases. Only one relapse (at 11 years) was reported in seven cases who underwent PORT, showing that PORT may have a role in selected cases of this indolent and slow-growing disease.

Verma et al. [120] suggest to refer patients with positive margins for PORT. PNI is not reported by the authors as a significant adverse prognostic factor for PLGA and is not considered a reason to administer PORT in patients with negative margins. Recommended RT doses are 66 Gy/33 fractions for microscopic residual disease and 70 Gy/35 fractions for gross residual disease [120].

From a literature search, Kimple et al. [121] reported that rates of recurrence after surgical excision without adjuvant radiation were 24.4% compared to 26.1% for surgical excision with adjuvant radiation therapy. However no information was available on selection criteria for PORT. The SEER database was queried for

HN-PLGA cases from 2001 to 2011 (460 cases) by Patel et al. [122]. Ten-year OS and disease-specific survival (DSS) were not significantly different for surgery alone and surgery plus PORT [122]. In a small group of patients treated with RT alone, DSS was 75%. Information were available only for 6 out of 11 patients; they were older and with advanced stage disease [122].

11.7.5 Radiotherapy for Epithelial-Myoepithelial Carcinoma

The SEER database (1973–2010) was queried for epithelial-myoepithelial carcinoma of the major salivary glands [123]. PORT was of no benefit, in terms of DSS, as compared to surgery alone in early stages (I–II); DSS was better after surgery plus RT vs surgery alone but not statistically significant in advanced stages (III–IV). However, stage was defined only in 93 out of 246 cases, and tumor size served as a proxy for clinical stage (tumor size of >4 cm had significant impact on survival). Furthermore, grading and margin status were not taken into account [123].

Therefore, no firm statement can be drawn on PORT indications.

11.7.6 Radiotherapy for Low-Grade Adenocarcinoma

A series of 51 patients with adenocarcinoma of the salivary gland, including 8 LG cases (unfortunately 15 patients had unknown grade), was reviewed [124].

Indications for PORT in low- to intermediate-risk adenocarcinoma of the salivary glands were aggressive features such as positive or close margins, PNI, angiolymphatic invasion, extensive extraglandular extension, or multiple lymph node involvement. Seventy-five percent and 62.5% of patients with IG and LG disease underwent PORT, respectively.

In general, treatment protocol at the authors' institution is to treat low- to intermediate-risk disease with surgery followed by radiation if aggressive features are determined. Although this treatment protocol is intuitive, adjuvant radiotherapy did not demonstrate a significant survival benefit; however, patients who received adjuvant therapy did reveal a trend toward better OS [124].

11.8 Benign Tumors: Pleomorphic Adenoma

11.8.1 Indications and Role of PORT

Pleomorphic adenomas account for 70–80% of benign SGTs and are especially common in the parotid gland [125].

Evidences of the role of PORT in pleomorphic adenoma after surgery come from various retrospective studies on institutional small series reporting on patients with primary disease [80, 126–129], recurrent disease [80, 130–136], or mixed cases [137, 138] and from a few review articles on the topic [139–143].

In Table 11.2 indications to RT, settings (primary treatment, recurrent tumor), treatments (surgery, surgery plus PORT), disease control, and follow-up duration are reported.

Primary RT is anecdotal; gross tumor is not irradiated primarily unless it is absolutely unresectable, since LC is relatively low in large tumor [138, 141].

Indications to PORT are controversial. Incomplete removal [128, 132]; gross residual disease [137]; tumor capsule rupture and spill [126, 128, 130, 132]; strict adherence and embedding of facial nerve [126, 132]; close [131], equivocal [137], or positive margins [126, 130, 131, 137]; and multiple [130] and multinodular [131] recurrences, all these features are reported as possible indications to RT after surgery.

The amount of disease left behind is of paramount importance to achieve LC both for primary and recurrent cases treated with surgery and PORT [135, 137, 138]. Hodge et al. analyzed LC in microscopic disease vs gross residual disease: the presence of macroscopic disease decreased LC of 37% [138]. This series was recently updated and a reduction of LC by 18% was observed [137].

The pattern of recurrence (uninodular vs multinodular) has been reported to influence LC after combined treatment as well. Renehan et al. found no difference in LC between surgery alone and surgery + RT for uninodular recurrences, while adjuvant RT improved results as compared to surgery alone for multinodular recurrences: authors concluded that uninodular recurrences per se should not be offered adjuvant RT [133]. In spite of the more aggressive disease pattern, LC for multinodular recurrences can be excellent: Renehan reported a 15-year LC of 96% [133], Leverstein observed recurrence in 16 patients with this pattern, and none developed a further recurrence after surgery plus RT [132].

Few retrospective series compared surgery alone vs surgery + RT. Improved LC for patients treated with adjuvant RT vs surgery alone in case of first treatment was reported by Robertson et al. [126].

Similarly, better LC for adjuvant RT vs surgery alone in recurrent cases was reported in other series [131, 133, 134].

In summary, if long natural history may favor wait and watch policy, the addition of PORT in selected cases can decrease the rate of locoregional recurrence (to less than 5%) and can reduce the chance of repeat surgery and damage to VII nerve [140].

11.8.2 Timing, Technique, Target Volume, and Schedules

Timing of radiotherapy is controversial. Whether to add RT after the first surgery rather after surgery for recurrence is a matter of debate.

Robertson et al. acknowledged the possible role of RT after primary surgery in reducing recurrence rates but emphasized the radio-induced toxicity and warned against delivering routinely RT [126].

On the contrary, Barton et al. stated that “patients having unsatisfactory surgery due to spill or residual tumor should have RT immediately and not delayed until local recurrence occurs because of the increased morbidity and the higher incidence of further recurrence” [128].

Table 11.2 Main characteristics and relative reported outcomes of studies on pleomorphic adenoma included in this chapter

Author	Year	Pri/rec	N. pts	TMT	FU	% LC	Subsets	Indications to RT
Dawson	1985	Pri	311	S+RT	10 min	92	n.r.	
Dawson	1989	Rec	29	S+RT	8.5 mean	79	n.r.	
Ravasz	1990	Rec	16	S+RT	11 med	94	n.r.	
		Pri	62	S+RT		100	n.r.	
Samson	1991	Rec	21	S+RT	5.9 mean	81		
			17			94	Microscopic tumor	
			4			25	Gross tumor	
Barton	1992	Pri	115	S+RT	14 med	91	n.r.	Incomplete removal, T spill
		Rec	62	S+RT	14 med	87	n.r.	
Liu	1995	Rec	17	S	12.5 med	6	n.r.	
			16	S+RT		82	n.r.	
Renehan	1996	Rec	63	S	14 med	76	n.r.	
			51	S+RT		92	n.r.	
Leverstein	1997	Rec	16	S+RT	8.8 med	100	Multinodular	Embedded FN, incomplete removal, multinodular rec, T spill
Carew	1999	Rec	20	S	7.3 med	71	n.r.	
		Rec	11	S+RT		100	n.r.	Close or positive marg, multiple rec
Hodge	2005	Pri/Rec	17	RT/S+RT	9.6 med	61	n.r.	Equivocal or positive marg, gross residual, T spill
			2	RT		0	n.r.	
			10	S+RT		80	Microscopic tumor	
			7	S+RT		43	Gross tumor	
Chen	2006	Rec	34	S+RT	17.4 med	94	n.r.	Multiple rec, positive marg, T spill
Wallace	2013	Pri/Rec	25	RT/S+RT	10.5 med	72	n.r.	Equivocal or positive marg, gross residual, [multinodular rec]
			16			75	Subclinical disease	
			9			56	Gross disease	
Patel	2014	Pri	21	S+RT	7.6 med	90	n.r.	Close or positive marg
Robertson	2014	Pri	53	S	6.4 med	79	n.r.	
			25	S+RT		96	n.r.	Positive marg, T capsule rupture, adherence to FN

Abbreviations; *Rec* recurrent tumors, *Pri* primary tumors, *N.pts* number of patients, *TMT* treatment, *S* surgery, *S+RT* surgery plus postoperative radiotherapy, *FU* follow-up, *FN* facial nerve, *rec* recurrences, *T* tumor, *marg* margins, *mean* mean, *med* median

Multiple irradiation techniques have been developed over the years, from the conventional wedged-paired fields to the three-field techniques, 3D-CRT, and more recently IMRT in its various forms. Its highly conformal dose distributions and reduction in doses to the surrounding normal tissues are hoped to translate into a reduction in both acute (skin and mucosal) and late (functional and cosmetic) toxicities [144].

Bolus was routinely placed over the surgical scar by Chen et al. [130]. In the Carew series, more than half of the recurrences had multiple nodules, and in more than 40% of the cases, the recurrence involved the scar of the previous surgical incision, a fact attributed to tumor spillage that may explain the suggestion for bolus application [131].

The treatment volume, in case of parotid origin, must include the operative bed and the whole parotid space [130, 145]. Treatment of the neck in benign adenomas is not recommended [130, 145].

To delineate more accurately the treatment volume, a fusion of the CT CE simulation scan with the preoperative MRI is suggested [145]. A postoperative MRI is similarly helpful, namely, in case of residual disease. In case of multinodular recurrences, all the nodules even the tiniest have to be contoured [145].

As for treatment dose, Patel [127] delivered a median dose of 57.6 Gy (range 55.8–69.96) with fractions of 1.8–2 Gy/die; similarly, Robertson gave 60 Gy in 30 fractions [126].

A dose of 50–60 Gy with a boost of 10–20 Gy in case of gross residual disease is suggested by Jardel et al. [145] with conventional fractionation. In the Wallace [137] series, 17 patients received once-daily external beam RT to a median total dose of 64.8 Gy (range, 56.5–70 Gy) and a median dose per fraction of 1.8 Gy. For Chen the median radiation dose was 50 Gy (range, 45–59.40) with conventional fractionation [130].

Target volume definition and RT dose distribution with postoperative VMAT in a case of recurrent multinodular pleomorphic adenoma of parotid gland are shown in Fig. 11.3.

11.8.3 Toxicity

A first concern when adding PORT is the increase of morbidity [140].

Robertson emphasized the radio-induced toxicities. Of the 25 patients who received PORT, 22 developed complications from RT [126]. The majority were troubled with permanent erythema and skin discoloration (21 cases) at the treatment site. Cases of xerostomia (2 patients), dysphagia (2 patients), temporary hearing loss (1 patient), persisting aural discharge (1 patient), and altered taste (1 patient) were also reported [126].

On the contrary, in the series of Patel, acute morbidity was limited to RTOG grades 1–2, and no patients experienced RTOG grade 2–4 late toxicities [127]. Similarly no patients developed severe complications subsequent to RT in the series by Wallace. Dental caries and transient facial nerve deficits were the most common complications [137].

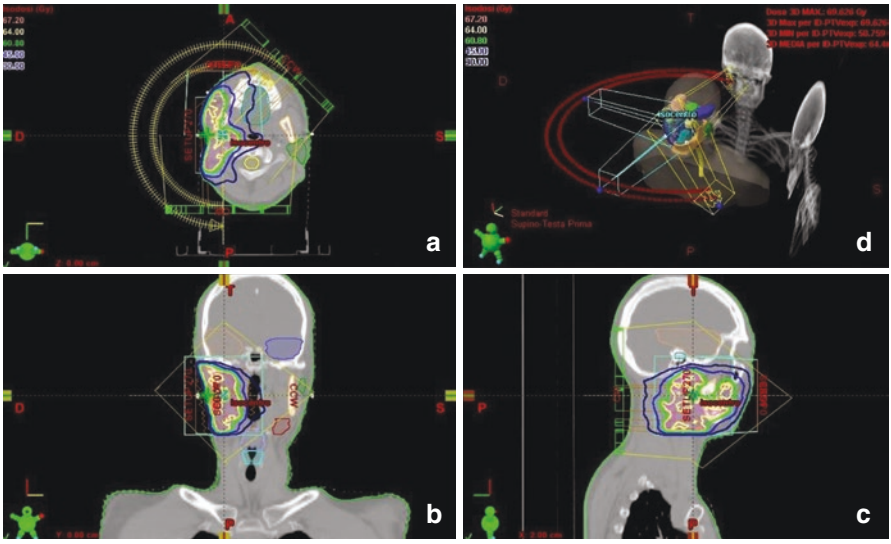

Fig. 11.3 Recurrent multinodular pleomorphic adenoma of the right parotid gland: treatment planning for postoperative VMAT dose 64 Gy. Figures (**a**–**c**), respectively, show axial (**a**), coronal (**b**), and sagittal (**c**) computed tomography (CT) simulation images. Planning target volume (PTV) (64 Gy), in red, includes the surgical bed with margins. Figure (**d**) shows a three-dimensional view of VMAT plan with arches

A second concern is the risk of radiation-induced malignant changes [140], especially in younger patients.

Malignant degeneration into carcinoma ex pleomorphic adenoma occurring in recurrent pleomorphic adenomas is reported in the literature with varying rates (0–16%) [133]. Two cases of malignant change in 25 patients (0.5%) were reported by Wallace [137] and Leverstein series [132], and 1 case out of 62 patients was reported by Barton [128].

Pleomorphic adenomas rarely progress to carcinoma in the absence of previous RT, but it is difficult to say which is the exact contribution of RT. Olsen and Lewis reported on 73 patients treated at the Mayo Clinic (Rochester, MN) for carcinoma ex pleomorphic adenoma, and 70 patients (96%) had no history of prior RT to the site of the tumor [128].

Fourteen patients were observed at the Christie with three or more recurrences in the parotid gland; in 3 out of 14 cases (0.42%), carcinomatous changes were noted [133]. Previous RT was delivered in all three patients. Number of recurrences and time of follow-up may be correlated to malignant transformation in addition to previous RT [133].

The rate of malignant transformation may be lower with PORT, being reported in 3–4% of the cases [140]. Second malignancies of different and possibly radio-induced tumors have been also occasionally reported [140]. In the Chen series, one patient developed a second LG salivary gland malignancy at approximately 14 years after completion of therapy [130].

Rare cases of secondary adenocarcinoma have been reported, although adenocarcinomas were also observed after surgery alone [140]. Dawson reported one malignant tumor probably radiation-induced, while the other cases were compatible with spontaneous malignant transformation of benign pleomorphic adenoma, although radiation may have played a role [129].

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