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CLINICAL INVESTIGATION **Head and Neck**

THE ROLE OF RADIOTHERAPY IN THE TREATMENT OF MALIGNANT SALIVARY GLAND TUMORS

Chris H. J. Terhaard, M.D., Ph.D.,* Herman Lubsen, M.D., Ph.D.,† Coen R. N. Rasch, M.D., Ph.D.,‡ Peter C. Levendag, M.D., Ph.D.,§ Hans H. À. M. Kaanders, M.D., Ph.D.,‖ Reineke E. Tjho-Heslinga, M.D.,¶ Piet L. A. van Den Ende, M.D.,# Fred Burlage, M.D.,** on behalf of the Dutch Head and Neck Oncology Cooperative Group (NWHHT)

*Department of Radiotherapy, University Medical Center, Utrecht, The Netherlands; †Department of ENT, University Medical Center, Utrecht, The Netherlands; ‡Department of Radiotherapy, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands; §Department of Radiotherapy, Rotterdam/Erasmus Medical Center, Daniel den Hoed, Rotterdam, The Netherlands; ‖Department of Radiotherapy, University Medical Center, Nijmegen, The Netherlands; ¶Department of Radiotherapy, University Medical Center, Leiden, The Netherlands; #Department of Radiotherapy, Maastro Clinic, Maastricht, The Netherlands; **Department of Radiotherapy, University Medical Center, Groningen, The Netherlands

Purpose: We analyzed the role of primary and postoperative low linear energy transfer radiotherapy in 538 patients treated for salivary gland cancer in centers of the Dutch Head and Neck Oncology Cooperative Group, in search for prognostic factors and dose response.
Methods and Materials: The tumor was located in the parotid gland in 59%, submandibular gland in 14%, oral cavity in 23%, and elsewhere in 5%. In 386 of 498 patients surgery was combined with radiotherapy, with a median dose of 62 Gy. Median delay between surgery and radiotherapy was 6 weeks. In the postoperative radiotherapy group, adverse prognostic factors prevailed. Elective radiotherapy to the neck was given in 40%, with a median dose of 50 Gy. Primary radiotherapy (n = 40) was given for unresectable disease or M_1, with a dose range of 28–74 Gy.
Results: Postoperative radiotherapy improved 10-year local control significantly compared with surgery alone in T_{3-4} tumors (84% vs. 18%), in patients with close (95% vs. 55%) and incomplete resection (82% vs. 44%), in bone invasion (86% vs. 54%), and perineural invasion (88% vs. 60%). Local control was not correlated with interval between surgery and radiotherapy. No dose–response relationship was shown. Postoperative radiotherapy significantly improved regional control in the pN_+ neck (86% vs. 62% for surgery alone). A rating scale for different sites, T stage, and histologic type may be applied to calculate the risk of disease in the neck at presentation, and so indicate the need for elective neck treatment. A marginal dose–response was seen, in favor of a dose ≥46 Gy. A clear dose–response relationship was shown for patients treated with primary radiotherapy. Five-year local control was 50% with a dose of 66–70 Gy.
Conclusions: Postoperative radiotherapy with a dose of at least 60 Gy is indicated for patients with T_{3-4} tumors, incomplete or close resection, bone invasion, perineural invasion, and pN_+. In unresectable tumors, a dose of at least 66 Gy is advisable. © 2005 Elsevier Inc.

Salivary gland cancer, Primary radiotherapy, Postoperative radiotherapy, Dose response, Local control, Regional control, Neck treatment.

INTRODUCTION

In the past salivary gland tumors were considered insensitive to radiotherapy. However, in several reports postoperative radiotherapy has been shown to improve locoregional control for salivary gland tumors (1–5). That makes a more conservative surgical approach conceivable for tumors when complete resection would result in poor cosmetic or functional outcome (6, 7). In 1984 Vikram *et al.* (8) suggested that when radiotherapy is used for inoperable adenoid cystic carcinoma it results in useful palliation, but rarely, if ever, cure is reached. However, more recent data show high locoregional cure rates for unresectable salivary gland tumors with the use of accelerated low LET treatment (9) and high LET treatment (10).

The Dutch Head and Neck Oncology Cooperative Group (NWHHT), in which head-and-neck groups of all University hospitals and the Netherlands Cancer Institute collabo-

Reprint requests to: Chris H. J. Terhaard, M.D., Ph.D., Department of Radiotherapy, UMC Utrecht, Heidelberglaan 100, 3583 CX Utrecht, The Netherlands. Tel: (+31) 30-25-08800; Fax: (+31) 30-25-81226; E-mail: C.H.J.Terhaard@azu.nl
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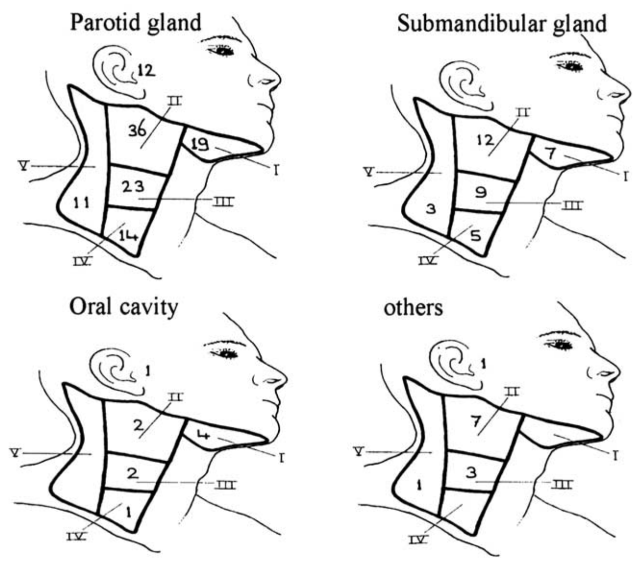

Fig. 1. Positive neck nodes (%) at first presentation, according to site and level (I–V).

rate, decided to perform a retrospective study of malignant salivary gland tumors, conducted by the first two authors of this article. In the Dutch situation a vast majority of head-and-neck patients is treated in the participating centers and the follow-up in these centers is very precise. After a review of the literature a comprehensive questionnaire was developed and filled in by the centers. All data were centrally stored and checked and analyzed with the same statistical methods and for the same endpoints. Tumors located in the nasal cavity were excluded.

General results of this study will be published elsewhere (11). In this article we will focus on the role of radiotherapy in the treatment of malignant salivary gland tumors, as follows: the role of primary radiotherapy as palliative (response) or curative treatment (locoregional control); the role of postoperative treatment for local and regional control, searching for prognostic factors as indicators for postoperative treatment; analysis of a possible dose–response relationship; and the role of radiotherapy in the elective treatment of the neck nodes.

METHODS AND MATERIALS

Patient characteristics

Data were collected on 498 patients treated with surgery with (n = 386) or without (n = 112) postoperative radiotherapy, and 40 patients treated with primary radiotherapy, in 3 combined with chemotherapy. Patients were treated during the period of 1984–1995. Mean follow-up was 76 months and 105 months for patients alive at the last follow-up.

The mean age was 59 years (range, 8–100 years) and 51% of the patients were male. The tumor was located in the parotid gland in 59%, in the submandibular gland in 14%, in the oral cavity in 23%, and elsewhere (pharynx, larynx) in 5%.

Figure 1 shows the distribution of positive neck nodes among the lymph node regions of the neck for the above-mentioned sites. Elective neck dissections were performed on 76% of the tumors of the submandibular gland (29% pN_+), on 23% of the tumors of the parotid gland (38% pN_+), and on 18% of the tumors of the oral cavity (24% pN_+). The number of pathologic nodes varied between 1 and 42; 1, 2, 3, and >3 positive nodes were detected in, respectively, 29%, 12%, 14%, and 45% of the node-positive patients. When we include the results of neck dissection, neck nodes were positive in 24% of the patients, pathologically negative in 16%, and clinically negative in 60%; the N stage was unknown in 2 patients.

In Table 1 the distribution of several possible prognostic factors among the three groups (surgery alone, surgery plus postoperative radiotherapy, and primary radiotherapy) is shown.

Patients treated with primary radiotherapy were significantly older, distant metastases at presentation were seen in 18%, and clinically positive neck nodes in 32% (particularly N_{2-3}). Tumor size was >4 cm in 72% of patients treated with primary radiotherapy. The tumor was located in the medial lobe of the parotid gland in 18 of 40, with complete or partial facial nerve weakness in 13, and was located in the larynx/pharynx in 10 of 40. In the primary radiotherapy group the histologic diagnosis (World Health Organization [WHO] 1972) adenoid cystic carcinoma (n = 13) and adenocarcinoma not otherwise specified ([NOS] n = 15) predominated.

The distribution of possible prognostic factors differed significantly for the postoperative group compared with the surgery alone group (Tables 1 and 2). In the postoperative group, significantly more male patients, significantly more clinical and or pathologically positive neck nodes, and significantly more locally advanced tumors were seen. In the surgery alone group, the tumor was located in 60% in the oral cavity, for the combined treatment group the location in the parotid gland prevailed (66%). To determine the histologic subtype the WHO 1972 classification was used. Mucoepidermoid carcinoma was predominantly treated with surgery alone; for adenoid cystic carcinoma and undifferentiated tumors, combination treatment was more often administered.

In Table 2 the distribution among the treatment groups of histopathologic parameters is shown. The postoperative group differed significantly compared with the surgery alone group in mean tumor size, percentage of perineural or blood vessel invasion, and the status of the resection margins. A neck dissection was performed in 41% of the patients treated with combination therapy and in 22% of the patients treated by surgery alone. In the postoperative group significantly more neck node metastasis and extranodal spread was noted.

Radiotherapy data

The delay between surgery and start of radiotherapy varied between 2 and 22 weeks (mean, 6.5 weeks, median, 6 weeks; Fig. 2). Patients were treated with local field only in 46%, local plus ipsilateral regional field in 45%, and bilaterally in 9%. Radiotherapy was administered with megavoltage equipment; photons were used in 56%, electrons in 12%, and a combination in 31%.

In the postoperative group, in general, patients were treated with 5 fractions of 2 Gy weekly (n = 298). A fraction dose of 1.8 Gy was used in 4 patients; between 2.2 Gy and 2.5 Gy was used in another 77 patients. Total dose to the primary tumor region ranged from 18–74 Gy, mean dose was 62.6 Gy and median dose was 62 Gy; in 98% 50 Gy or more was delivered (Fig. 3). The total local dose depended on the status of the resection margins (mean dose of 60.7 Gy for complete, 62.4 Gy for close, and 64.0 Gy for

Table 1. Distribution of prognostic factors among the given treatment modalities

	Surgery + postoperative RT (n = 386)	Surgery alone (n = 112)	Primary RT (n = 40)	p Value
Mean age (years)	58	60	68	0.002
Percent male	55	38	55	0.005
Percent with pain	26	24	55	<0.001
Percent clinical or pathological N_+	27	8	32	<0.001
Percent T_1–T_2–T_3–T_4	22–51–21–6	52–35–10–4	5–24–32–40	<0.001
Percent M_1	0.3	1	18	<0.001
Localization (%)				
Parotid	66	33	63	<0.001
Submandibular	18	3	5	
Oral cavity	14	60	8	
Others	3	5	25	
WHO 1972 classification (%)				<0.001
Acinic cell ca.	13	13	3	
Mucoepidermal carcinoma	13	34	5	
Adenoid cystic carcinoma	28	14	33	
Adenocarcinoma, NOS	21	27	38	
Carcinoma, ex pl. adenoma	9	5	—	
Squamous cell carcinoma	6	4	10	
Undifferentiated carcinoma	8	1	10	

Abbreviations: RT = radiation therapy; WHO = World Health Organization; NOS = not otherwise specified; ex pl. = ex pleomorphic.

incomplete resection margin, $p < 0.001$). Overall treatment time varied between 1 and 94 days, with a mean of 45 days. To calculate equivalent response dose (ERD) the linear quadratic model was used: $ERD = d.n. (1 + [d/(\alpha/\beta]) - ln2/\alpha) \cdot (OTT/Tpot)$, where $\alpha/\beta = 10$, Tpot assumed 5 days, d = fraction size, n = number of fractions, $\alpha = 0.3$, OTT = overall treatment time, Tpot = potential doubling time.

In the primary radiotherapy group, a wide range of dosages were used. In 29 patients, fractions between 1.8 and 2.5 Gy were used with a mean total dose of 63 Gy (range, 28–74 Gy).

Table 2. Distribution of histological parameters, derived from the resection specimen, among the different treatment modalities

	Surgery + postoperative RT	Surgery alone	p Value
Mean pathology tumor size (mm)	30	21	<0.001
Resection margin local (%)			<0.001
Complete	30	64	
Close (<5 mm)	22	11	
Incomplete	46	23	
Percent perineural invasion	41	22	0.002
Percent blood vessel invasion	24	8	0.003
Percent bone invasion	5	10	0.02
Percent skin invasion	6	5	ns
Resection margin regional (%)			ns
Complete	86	96	
Close/incomplete	9	—	
Unclear	4	4	
Extranodal (EN) disease (%)			0.03
Node negative	40	64	
Node positive, EN negative	17	24	
Node positive, EN positive	36	8	
Node positive, EN?	7	4	
Number of nodes (%)			0.02
0	41	64	
1	15	24	
2–3	15	8	
>3	28	4	

Abbreviation: ns = not significant.

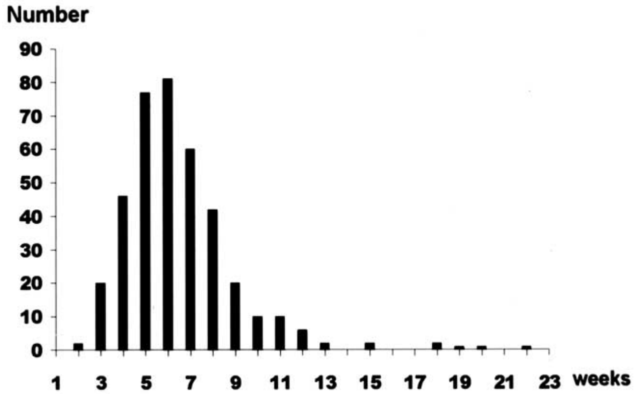

Fig. 2. Interval between surgery and postoperative radiotherapy.

In the remaining group, palliative doses were used with a fraction size between 3 and 8 Gy and a total dose between 20 Gy and 52 Gy.

Elective radiotherapy of the neck nodes was given in 40% (n = 120) of the patients with a cN_0 neck. In general, except for tumors of the larynx and pharynx, only the ipsilateral neck nodes were treated. Tumors of the submandibular gland, larynx and pharynx, squamous cell and undifferentiated tumors predominated. Median elective dose to the N_0 neck nodes was 50 Gy in a median of 37 days, 78% of the patients received ≥46 Gy. Mean postoperative dose for positive neck nodes was 61 Gy in a median 44 days (n = 89); 94% of the patients received ≥50 Gy, and 73% ≥60 Gy.

Statistics

The statistical analysis was performed with the SPSS/PC program version 10.1. The chi-square test and Mann-Whitney test were used to compare groups for nominal and ordinal variables, respectively. The Kaplan-Meier method was used to fit actuarial curves, in combination with the log rank test for comparison of groups. The Cox proportional hazards regression analysis was used for multivariate analysis. For the resulting prognostic factors, the relative risk (RR) was estimated with a 95% confidence interval (CI).

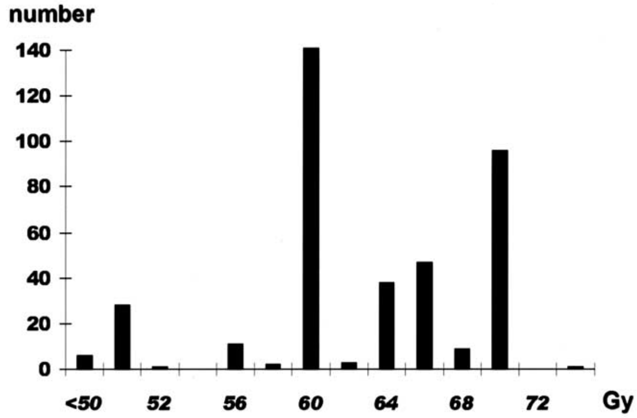

Fig. 3. Dose distribution postoperative local radiation field.

Table 3. Results: Risk of positive neck nodes (%), according to summation of scores (T: T_1 = 1; T_2 = 2; T_{3-4} = 3; and histological type: acinic/adenoid cystic/carcinoma ex pleomorphic adenoma = 1; mucoepidermoid carcinoma = 2; squamous cell/undifferentiated carcinoma = 3) and site

Summation: T score + histological type score	Parotid gland	Submandibular gland	Oral cavity	Other locations
2	4%	0%	4%	0%
3	12%	33%	13%	29%
4	25%	57%	19%	56%
5	33%	60%	—	—
6	38%	50%	—	—

RESULTS

Prognostic factors for positive neck nodes

We investigated the association between prognostic pretreatment factors and the risk of metastasis of the neck nodes. Independent prognostic factors for the presence of positive nodes were T stage (T_1 15%, T_2 26%, T_3 33%, and T_4 33%; $p = 0.006$), site of the primary tumor (oral cavity 9%, parotid gland 25%, submandibular gland 42%, other locations 36%; $p < 0.0001$). In the regression analysis, the RR for T_2 vs. T_1 was 2.5; the RR for T_{3-4} vs. T_1 was 3.4; and the RR for mucoepidermoid, squamous cell/undifferentiated compared with acinic cell/adenoid cystic/carcinoma ex pleomorphic adenoma was, respectively, 2.2 and 3.4.

We worked out a rating scale to score the risk of positive neck nodes based on T status (score, 1–3) and histologic type (score, 1–3). By summation of these scores, we end up with a table of results (total score, 2–6; Table 3).

Local control

Surgery plus or minus postoperative radiotherapy. Actuarial local control rates after 5 and 10 years were, respectively, 84% and 76% for surgery alone and 94% and 91% for combined surgery and radiotherapy ($p = 0.0005$). Independent prognostic factors for local control were treatment, with a RR for surgery alone compared with combined treatment of 9.7, clinical tumor size, tumor location, status of the resection margins, and bone invasion (11).

Local control after 10 years was significantly better with combined treatment for T3 and T4 tumors (84% vs. 18% for surgery alone, $p < 0.001$; Fig. 4), not significantly better for T1 (95% vs. 83%% with surgery alone), and T2 (91% vs. 88% for surgery alone). For all tumor locations, except the oral cavity, local control was significantly higher with combined treatment (parotid gland 88% vs. 51%, submandibular gland 91% vs. 67%, oral cavity 98% vs. 91%, and other locations 90% vs. 30% for surgery alone). For complete resection margins 10 years local control was 90% with surgery alone vs. 98% for combined therapy (p = not significant). Combined treatment significantly improved 10-year local control for close resection margin (95% vs. 55% for surgery alone, $p = 0.003$) and incomplete resection

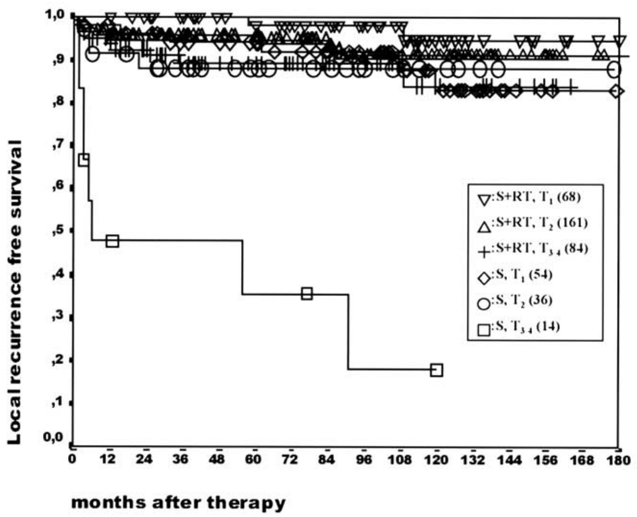

Fig. 4. Local recurrence-free survival depending on T status and therapy. (S+RT = surgery plus radiotherapy.)

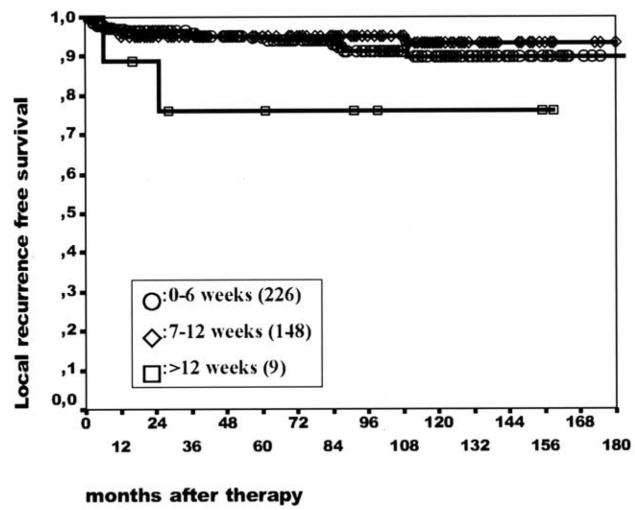

Fig. 6. Local recurrence-free survival and interval surgery and postoperative radiotherapy.

(82% vs. 44% for surgery alone, $p < 0.001$; Fig. 5). For tumors with pathologic confirmed bone invasion 10-year local control was 54% with surgery alone vs. 86% for combined therapy ($p = 0.04$). Ten-year local control for tumors with perineural invasion was 60% after surgery alone, and 88% after combined treatment ($p = 0.01$).

In the surgery alone group, the best local control rate (52 of 55) was achieved for patients treated for a T1 or T2 tumor, with a complete resection and with no bone invasion.

No significant correlation was shown between local control and interval between surgery and radiotherapy. Treatment after 12 weeks resulted in a slightly lower local control rate (Fig. 6), but this was not statistically significant. No dose–response relationship was detected for local control, using total dose or equivalent dose using the linear quadratic model as parameter. Since the dose delivered was adapted to the status of the resection margins, a dose–response relationship was evaluated for patients irradiated for incomplete resection only. Also for this subgroup no dose–response relationship was seen, either for total dose alone, or for equivalent dose using the LQ model (Fig. 7).

Primary radiotherapy. Complete, partial, and less than 50% local response rates 3–6 weeks after radiotherapy were respectively 38%, 30%, and 30%. The correlation between response and local control is shown in Table 4. A clear dose–response relationship was observed in the primary radiotherapy group with a 50% local control after 5 years for a dose $\geq$66 Gy ($n = 20$) vs. 0% for $<$66 Gy ($n = 18$, $p = 0.0007$; Fig. 8).

Regional control

Independent factors for regional control were treatment, with a RR for surgery alone compared with combined

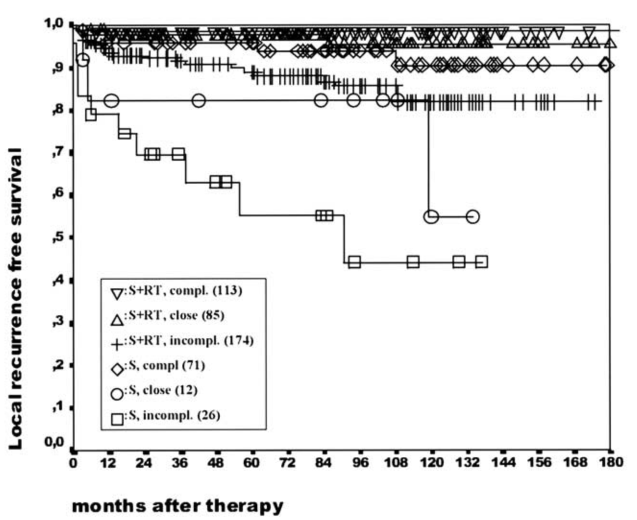

Fig. 5. Local recurrence-free survival depending on status of resection margins and therapy. (S+RT = surgery plus radiotherapy; compl. = complete; incompl. = incomplete.)

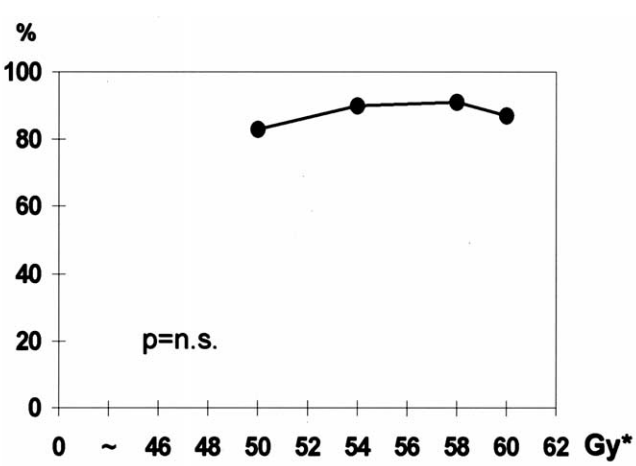

Fig. 7. Radiotherapy after incomplete resection: dose–response (*linear quadratic–dose equivalent, potential doubling time [Tpot] = 5) for 5-year local control. (n.s. = not significant.)

Table 4. Primary radiotherapy, correlation between response 3–6 weeks after radiotherapy and local control

Local response	Five-year actuarial local control
Complete, $n = 14$ (38%)	69%
>50%, $n = 11$ (30%)	11%
<50%, $n = 11$ (30%)	9%
Unknown, $n = 1$ (3%)	0/1

treatment of 2.3, N status and WHO 1972 classification (11).

For clinical/pN_0 tumors, actuarial regional control after 10 years was 89% for surgery alone and 93% for combined treatment (p = not significant). For pN_+ actuarial 5-year regional control was 62% for surgery alone and 86% for combined treatment ($p = 0.03$).

Neck node control after postoperative locoregional radiotherapy ($n = 22$) was 83% after 10 years for pN_1, and 57% after no or only local postoperative radiotherapy ($n = 10$, $p = 0.04$).

Elective radiotherapy to the N_0 neck

A slight dose–response relationship was shown for radiotherapy to the N_0 neck. Regional control after 10 years was 88% for a dose of <46 Gy ($n = 27$), and 96% for ≥46 Gy ($n = 93$, $p = 0.07$). Application of the linear quadratic model did not result in a more significant dose–response curve.

Postoperative radiotherapy for the N_+ neck

No dose–response correlation was shown for postoperative radiotherapy of the N_+ neck, neither with the variable total dose, nor with the application of the linear quadratic model.

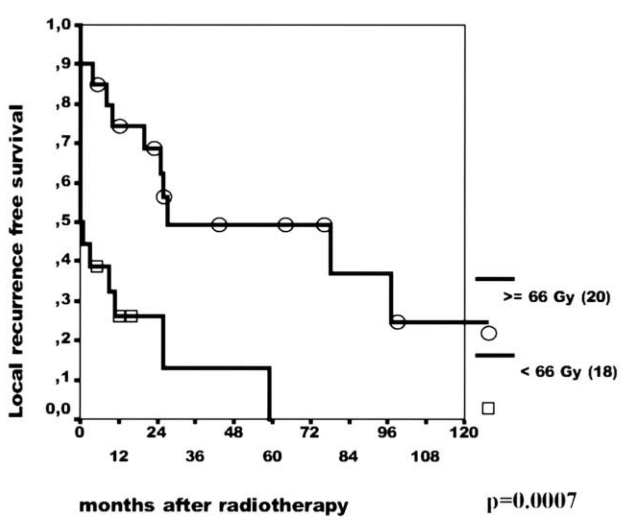

Fig. 8. Primary radiotherapy: local recurrence-free survival depending on tumor dose.

Primary radiotherapy for the N_+ neck

Twelve patients with positive neck nodes received primary radiotherapy. For a dose of 50 Gy or less neck node control was 0/6 compared with 5/6 for a dose of 66–70 Gy ($p = 0.003$).

DISCUSSION

Indications for postoperative radiotherapy

The only randomized study in salivary gland tumors is conducted for patients with an unresectable tumor (10). Evidence of a positive role of postoperative radiotherapy as an independent factor in locoregional control for salivary gland tumors is based on retrospective studies (2–5). In a matched-pair analysis by Armstrong *et al.* (1) postoperative radiotherapy significantly improved locoregional control and determinate survival for Stages III and IV, and for patients with positive node metastases. As a retrospective study, our study has some shortcomings. Nonetheless, the patient characteristics, histologic and radiotherapy parameters, and data concerning the follow-up are well documented. The median follow-up period was 105 months for those patients who were alive at the time of the last follow-up. Long-term follow-up is recommended because failures may appear after 5 years (12–13), as also shown in our study. In our study postoperative radiotherapy was the most important factor for local control and regional control, with a RR of, respectively, 9.7 and 2.3 for surgery alone vs. combined therapy (11).

Local control was 91% after 10 years, which is comparable with some reported series (2, 3, 6, 13, 14), but more favorable than those reported by others (1, 15, 16). We found local control to be improved significantly in patients treated with postoperative radiotherapy for advanced T stage (Fig. 5), incomplete or close resection margins (Fig. 6), or bone invasion. For patients with neither of these unfavorable prognostic factors, surgery alone resulted in a 95% 5-years and 90% 10-year local control. In this selection tumors of the oral cavity predominated. Local control was significantly higher for oral cavity tumors, as reported by Le *et al.* (13). In univariate analysis, local control depended on perineural invasion, and improved significantly for patients treated with postoperative radiotherapy (from 60% to 88% after 10 years). However, in multivariate analysis, in our study, perineural invasion was no independent factor for local control (11).

Based on our results and data from the literature we recommend postoperative radiotherapy for T3–4 tumors (13, 14, 17–20), close or incomplete resection (2, 3, 6, 7, 13, 14, 17, 18), bone involvement (17), and perineural invasion (8, 16). Histology was in our study not an independent factor for local control. Many authors recommend postoperative radiotherapy for "aggressive histology" (18) and for high-grade lesions (2, 6, 14, 17, 20); however, most studies are based on univariate analysis only. Histology was not an independent prognostic factor for disease-free survival for parotid tumors in a publication of van der Poorten *et al.* (21).

Dose–response in postoperative radiotherapy?

The time factor plays an important role in combined treatment of head-and-neck cancer. Peters *et al.* (22) postulated that after surgery residual tumor cells will repopulate at their maximal potential without delay. Because salivary gland tumors generally grow slowly, one might expect less adverse effect of delay between surgery and postoperative radiotherapy. Until 12 weeks between surgery and radiotherapy in our study, no adverse effect of delay was seen (Fig. 6); this in contrast with a study concerning minor salivary glands by Garden *et al.* (6). Inclusion of the time factor in the linear-quadratic formula in our study did not result in a more significant dose–response relationship. This suggests that the time factor plays a less important role in salivary gland tumors compared with other head-and-neck tumors.

No significant relation between dose and local control was shown in our study. However, in 98% the dose was more than 50 Gy, the median dose was 62 Gy, and the total dose was adjusted to the status of the resection margin. In a subgroup of patients with radiotherapy (≥60 Gy in 92%) for incomplete resection also no significant dose–response relationship was shown (Fig. 7). North *et al.* (3) and Storey *et al.* (14) showed no dose–response relationship for the same median dose. Garden *et al.* (2) found a trend toward improved local control rate in incomplete resected parotid carcinoma for a dose >60 Gy, comparable with data for incomplete resected adenoid cystic carcinoma by Miglianico *et al.* (16), for incomplete resected mucoepidermoid carcinoma by Hosokawa *et al.* (7), and for minor salivary gland tumors by Jenkins *et al.* (19). Based on our study and the literature, a dose of 60 Gy will be sufficientl for high-risk patients a dose of ≥65 Gy (2, 13, 15, 16), and for gross residual disease a dose of 70 Gy (15) may be advisable.

Guidelines for treatment of the neck nodes

The risk of occult nodal disease, and so the need for elective treatment of the neck nodes, depended on the T stage and the histologic type of the tumor, which is in accordance with data from Regis de Brito Santos *et al.* (23) and McGuirt *et al.* (24). Tumors more than 4 cm in size and high-grade tumors were independent risk factors for occult metastases in a study by Armstrong *et al.* (25) and Rodriguez-Cuevas *et al.* (26). Parotid tumors with facial paralysis are associated with a high percentage of occult lymph node metastases (27, 28).

At first presentation, neck nodes were positive particularly in levels I–III. For patients with 3 or fewer positive nodes, level IV and level V were positive in less than 10% of the cases. Positive neck nodes were diagnosed in 1 of 3 elective neck dissections; only 21% of these pN_+ patients had more than 3 nodes. Therefore, in elective treatment of the neck, at least level I, II, and III should be included, in accordance with the guidelines of Armstrong *et al.* (25).

When the local prognostic factors point to a need for postoperative radiotherapy, inclusion of the neck nodes may be based on the risk estimates shown in Table 3. According to Table 3, elective treatment of the neck nodes is indicated for almost all submandibular tumors, except for T_1 acinic or T_1 adenoid cystic tumors. For parotid tumors, the decision to treat the neck nodes will depend on the T stage and the histologic type, and will be indicated by a score of at least 4 (Table 3). Elective treatment of the neck for tumors of the oral cavity is seldom indicated.

No dose–response relationship was seen in the elective treatment of the neck, although there was a trend to impaired regional control rate for a dose <46 Gy. We recommend a dose of 46–50 Gy.

In our study postoperative radiotherapy for the *pN_+ neck* significantly improved regional control, even in case of pN_1. We found no dose–response relationship; however, most patients were treated with 60 Gy or more. In case of more than 3 positive nodes at presentation, in about 50% of the patients, level IV and level V were involved. Among patients with a positive neck node at presentation, 1 positive neck node was found in the neck dissection specimen in only 13% of the cases, and 3 or more positive nodes were found in 60% of the cases. Therefore, when planning curative treatment of the positive neck nodes, level I–V should be included.

Primary radiotherapy

Primary radiotherapy for salivary gland tumors generally is offered to unresectable cases or to patients with distant metastases at presentation, like in our study (Table 1). In our study a clear dose–response-relationship was shown (Fig. 8), with a 5-year local control rate of 50% with a dose of 66–70 Gy. However, recurrences after 5 years were seen. This figure is more favorable than those reported by others using conventional photon or electron therapy, with locoregional control rates in these studies of around 25% (10, 15, 29, 30). Accelerated hyperfractionated photon therapy for a total dose of 65–70 Gy may result in a local control rate of 85%, as shown by Wang *et al.* (9). The follow-up in that series was, however, rather short, and, to our knowledge, no update has been reported.

The low growth fraction and long doubling time make salivary gland tumors sensitive to high linear energy transfer radiotherapy. The calculated high radiobiological effect for salivary gland tumors makes them particularly favorable for neutron therapy (31). In the final report of the Amsterdam fast neutron therapy project a 65% persistent local control rate for unresectable salivary gland tumors was found (32). Neutron therapy was superior to photon therapy in the randomized Radiation Therapy Oncology Group–Medical Research Council (RTOG-MRC) trial concerning unresectable tumors, with a 10-year locoregional control rate of, respectively, 56% and 17% (10). Most published data for neutron therapy concern adenoid cystic carcinoma, with local control rates between 65% and 75% (29, 33–35). Severe late complication rate after neutron therapy, however, is higher compared with photon therapy. The second problem concerns lack of availability of neutron therapy facilities in most countries. In that case we recommend for unresectable salivary gland tumors photon therapy with a total dose of 70 Gy. Improvement of the results by accelerated hyperfractionated radiotherapy should be tested in a randomized trial (9). A new opportunity for cure of unresectable salivary gland tumors is a combination of photons and carbon ion radiotherapy. The three-year local control rate was 65% for adenoid cystic carcinoma, without late complications, in a study by Schulz-Ertner *et al.* (36); however, the number of patients was small, and the follow-up was short.

Technical improvements

In our study parotid gland tumors were treated with ipsilateral wedge pair fields, in some cases combined with electrons, or electrons only. Yaparpalvi *et al.* (37) concluded from their study that ipsilateral wedge pair fields, three-field and mixed electron-photon beam techniques resulted in the most optimal dose distribution regarding the target area and normal tissues. Further reduction in the dose received by the normal tissues may be reached by three-dimensional radiotherapy (38). Intensity-modulated radiotherapy should enable dose escalation in the parotid area, resulting in increased uncomplicated tumor control (39).

CONCLUSION

Postoperative radiotherapy for salivary gland tumors is indicated after close or incomplete resection, pathology-confirmed bone or perineural invasion, and T_{3-4} tumors. A dose of at least 60 Gy is recommended. The decision to treat the neck nodes electively should be based on T stage and histologic type of the tumor. A dose of at least 46 Gy at levels I–III is recommended. Postoperative radiotherapy is indicated for a pN_+ neck. Levels I–V should be treated with a dose of at least 60 Gy for the level with positive nodes. As primary radiotherapy with curative intent, a dose of 66–70 Gy may result in 50% 5-year local control.

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