Radiotherapy Alone or Combined with Surgery for Salivary Gland Carcinoma

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BACKGROUND. The authors analyzed the outcomes of patients treated with radiotherapy (RT) alone or combined with surgery for carcinoma of the salivary glands.
METHODS. Between October 1964 and June 2003, 224 previously untreated patients were treated with curative intent with RT alone ($n = 64$) or combined with surgery ($n = 160$) at the University of Florida College of Medicine (Gainesville, FL). The median follow-up period was 5.0 years (range, 0.4–31.6 years).
RESULTS. The 10-year local control rate was 75%. Multivariate analysis of local control revealed that T classification ($P < 0.0001$) and treatment group ($P < 0.0001$) impacted this end point. Patients treated with surgery and adjuvant RT had improved local control compared with patients treated with RT alone. The 10-year locoregional control rate was 68%. Multivariate analysis of locoregional control revealed that overall stage ($P < 0.0001$) and treatment group ($P = 0.0002$) significantly influenced this end point. The 10-year distant metastasis-free survival rate was 68%. Multivariate analysis of distant metastasis-free survival revealed that overall stage ($P < 0.0001$) significantly influenced this end point. The 10-year cause-specific and overall survival rates were 57% and 44%, respectively. Multivariate analysis of cause-specific survival revealed that overall stage ($P < 0.0001$) significantly impacted this end point. Twenty-three patients (10%) experienced severe complications.
CONCLUSIONS. A substantial proportion of patients with salivary gland carcinoma were cured with surgery combined with adjuvant RT. RT alone was used for patients with unresectable tumors and cured approximately 20% of those with advanced-stage disease. The probability of cure was influenced by the extent of disease and treatment group. ***Cancer* 2005;103:2544–50.**

KEYWORDS: radiotherapy, salivary gland, surgery, multivariate analysis, adjuvant chemotherapy.

Salivary gland malignancies are uncommon and comprise < 3% of newly diagnosed head and neck carcinomas in North America annually.[1] The incidence varies from 1.5 to 4.0 per 100,000 persons per year.[1] Men and women are affected equally.[1,2] The majority of salivary gland carcinomas occur in the parotid.[1,2] Parotid tumors are more likely to be benign, compared with those arising in other sites where the probability of malignancy is ≥ 50%.[1]

Traditionally, surgery has been the mainstay of treatment for salivary gland carcinomas. Patients with low-grade neoplasms are usually treated with surgery alone if complete excision can be achieved.[3] Patients with high-grade carcinomas, as well as those with positive margins, usually receive adjuvant postoperative radiotherapy (RT).[4–11] Patients with incompletely resectable tumors are usually treated with RT alone. The latter two groups of patients are the focus of the current article.

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A number of treatment-related issues continue to be the subject of debate, including the impact of adjuvant RT on outcome, the efficacy of RT alone, the effectiveness of neutron RT compared with conventional photon/electron RT, and the role of adjuvant chemotherapy. Addressing these issues is all the more difficult because of the relative rarity of salivary gland carcinomas and the variable natural history of the different histologies.[2–4,12,13] The aim of the current article is to analyze the outcomes of patients treated for salivary gland carcinomas at the University of Florida College of Medicine (Gainesville, FL) to better define the optimal management of this heterogeneous disease.

MATERIALS AND METHODS

Between October 1964 and June 2003, 224 patients with previously untreated salivary gland carcinomas were treated with curative intent at the University of Florida with RT alone (n = 64) or combined with surgery (n = 160). Patients with tumors arising from the lacrimal gland, trachea, cervical esophagus, or from an unknown primary site were excluded. The current study is part of a RADTRAC outcomes study approved by the institutional review board.

The study cohort comprised 131 men and 93 women with a median age of 5.8 years (range, 13–89 years). The median follow-up for patients was 5.0 years (range, 0.4–31.6 years). The median follow-up for living patients was 8.3 years (range, 0.9–31.6 years). At 5 years, 29 and 82 patients were alive after RT alone or combined with surgery, whereas 16 and 41 patients were alive, respectively, at 10 years. Patients were clinically staged according to the 2002 American Joint Committee on Cancer (AJCC) staging system.[14] The characteristics of the patient population are shown in Table 1. Patients with squamous cell carcinomas were not included in the current study because the majority of these patients are likely to have metastasis to the parotid lymph nodes compared with patients with primary salivary gland carcinomas. In general, patients believed to have completely resectable tumors underwent surgery initially and received postoperative RT because of close or positive margins, involved regional lymph nodes, high-grade histology, perineural invasion, and/or endothelial-lined space invasion. Patients with completely resected low-grade carcinomas did not receive adjuvant RT and are not included in the series. A small subset of patients with marginally resectable tumors underwent preoperative RT followed by surgery. RT alone was usually reserved for patients with advanced-stage, incompletely resectable tumors. A small subset of patients with earlier stage lesions received RT alone because of comorbid conditions or because the functional deficit associated with resection was believed to be suboptimal. Seven patients received adjuvant chemotherapy as part of their initial treatment.

RT was administered once daily to 143 patients, and twice daily to 81 patients. A continuous-course

TABLE 1
Patient Population (n = 224)

Variables	No. of patients (%)
Major site	
Parotid	85 (38)
Submandibular	15 (7)
Minor site	
Oral cavity	48 (21)
Oropharynx	23 (10)
Larynx	3 (1)
Hypopharynx	2 (1)
Paranasal sinus	20 (9)
Nasal cavity	16 (7)
Nasopharynx	7 (3)
Parapharyngeal space	4 (2)
Other	1 (1)
Histology	
Adenoid cystic carcinoma	96 (43)
High-grade mucoepidermoid carcinoma	50 (22)
Low-grade mucoepidermoid carcinoma	7 (3)
Acinic cell carcinoma	5 (2)
High-grade adenocarcinoma	44 (20)
Low-grade adenocarcinoma	9 (4)
Lymphoepithelioma	1 (1)
Carcinoma expleomorphic adenoma	12 (5)
T classification	
T1	49 (22)
T2	58 (26)
T3	34 (15)
T4	83 (37)
N classification	
N0	173 (77)
N1	14 (6)
N2	35 (16)
N3	2 (1)
Overall stage	
I	42 (19)
II	40 (18)
III	36 (16)
IVA	77 (34)
IVB	29 (13)
Surgery	
None	60 (27)
Primary site	105 (47)
Primary site and neck dissection	55 (24)
Neck dissection (included in RT-alone group for analysis)	4 (2)
RT	
RT alone	64 (29)
Preoperative RT	12 (5)
Postoperative RT	148 (66)
Adjuvant chemotherapy	
No	217 (97)
Yes	7 (3)

RT: radiotherapy.

technique was used for 207 patients, and a split-course technique was used for the remaining patients. The split-course technique was used between 1970 and 1974 and was subsequently abandoned. The median external-beam doses were as follows: RT alone, 74.0 gray (Gy; 50.0–79.2 Gy); postoperative RT, 66.0 Gy (10.5–85.0 Gy); and preoperative RT, 59.3 Gy (43.7–64.8 Gy). All patients received photon and/or electron RT; no patient was treated with neutrons. An interstitial implant was combined with external-beam RT in 7 patients.

Surgery consisted of resection of the primary tumor in 105 patients, resection of the primary cancer combined with neck dissection in 55 patients, and neck dissection alone in 4 patients. Patients who received neck dissection combined with RT alone to the primary site are included in the RT-alone group for the various outcomes analyses. The extent of the resection varied with the site and extent of the tumor. The median interval between surgery and RT was 36 days (range, 16–189 days). Resection margins were negative in 50 patients, microscopically positive in 99 patients, and macroscopic residual tumor was left in 11 patients.

The neck was clinically negative in 173 patients at diagnosis. The decision whether to observe or electively treat the neck depended on the primary site, histology, T classification, and philosophy of the attending physicians. The N0 neck was observed in 42 patients, electively dissected in 11 patients, and electively irradiated in 120 patients.

Complications were coded as severe if they necessitated hospitalization, surgical intervention, or were fatal.[15]

The Kaplan–Meier product-limit method was used to calculate the rates of local control, locoregional control, distant metastasis-free survival, cause-specific survival, and overall survival.[16,17] A Cox proportional hazards regression analysis of various end points was performed using eight explanatory variables.[18] Explanatory variables included in the multivariate analyses were as follows: gender, site (major vs. minor), histology (high-grade mucoepidermoid, adenoid cystic carcinoma, intermediate or high-grade adenocarcinoma, carcinoma expleomorphic adenoma, and other vs. low-grade mucoepidermoid, low-grade adenocarcinoma, and acinic cell carcinoma), T classification (T1–T3 vs. T4), N classification (N0 vs. N positive), overall stage (I–III vs. IV), perineural invasion (none or incidental vs. clinical), and treatment group (surgery and adjuvant RT vs. RT alone). The histologic group "other" included high-grade carcinoma expleomorphic adenoma ($n = 12$) and lymphoepithelioma ($n = 1$). Clinical perineural invasion suggests paresis of a named nerve at presentation. Too few patients received adjuvant chemotherapy to include it in the analyses.

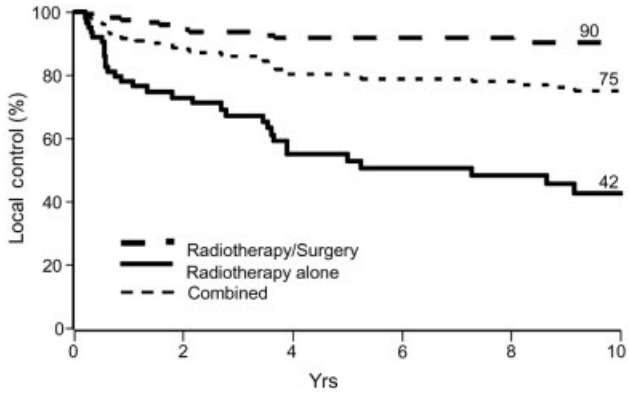

FIGURE 1. Local control rates after surgery and adjuvant radiotherapy, RT alone, and for the overall group. The 10-year local control rates were 90%, 42%, and 75%, respectively.

RESULTS

Time to Disease Recurrence

One hundred one patients developed disease recurrence after treatment (86% of disease recurrences were observed within 5 years of treatment and 95% were observed within 10 years).

Local Control

Figure 1 shows the rates of local control for the overall group as well as the subsets of patients treated with RT alone and surgery plus adjuvant RT. The 10-year local control rates for surgery and adjuvant RT compared with RT alone were as follows: T1–T3, 96% versus 75% ($P = 0.0003$); T4, 70% versus 21% ($P = 0.0004$); and overall, 90% versus 42% ($P < 0.0001$). Multivariate analysis of local control revealed that T classification ($P < 0.0001$) and treatment group ($P < 0.0001$) significantly influenced this end point.

Locoregional Control

The locoregional control rates for the overall groups and the subsets of patients treated with RT alone or surgery and adjuvant RT are shown in Figure 2. The 10-year locoregional rates for surgery and adjuvant RT compared with RT alone were as follows: I–III, 89% versus 70% ($P = 0.0109$); IV, 66% versus 24% ($P = 0.0019$); and overall, 81% versus 40% ($P < 0.0001$). Multivariate analysis of locoregional control revealed that overall stage ($P < 0.0001$) and treatment group ($P = 0.0002$) significantly impacted this end point.

Distant Metastases

The distant metastasis-free survival rates for the overall group and for the subset of patients treated with RT

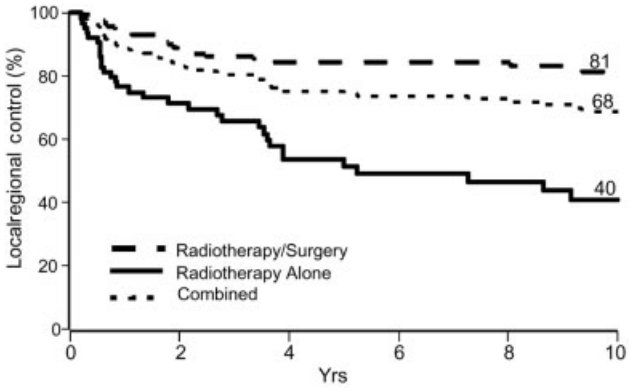

FIGURE 2. Locoregional control rates after surgery and adjuvant radiotherapy (RT), RT alone, and for the overall group. The 10-year locoregional control rates were 81%, 40%, and 68%, respectively.

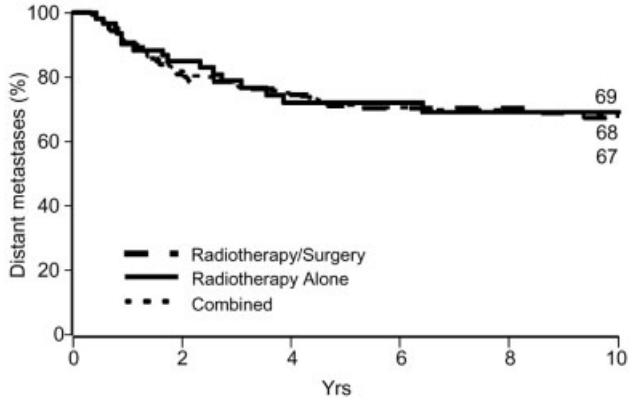

FIGURE 3. Distant metastasis-free survival rates after surgery and adjuvant radiotherapy (RT), RT alone, and for the overall group. The 10-year distant metastasis-free survival rates were 67%, 69%, and 68%, respectively.

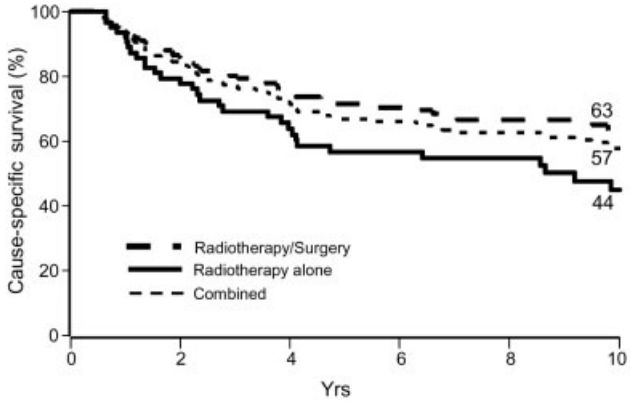

FIGURE 4. Cause-specific survival rates after surgery and adjuvant radiotherapy (RT), RT alone, and for the overall group. The 10-year cause-specific survival rates were 63%, 44%, and 57%, respectively.

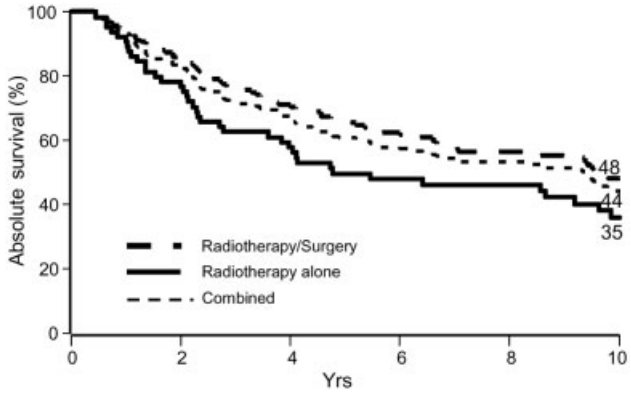

FIGURE 5. Overall survival rates after surgery and adjuvant radiotherapy (RT), RT alone, and for the overall group. The 10-year overall survival rates were 48%, 35%, and 44%, respectively.

alone and surgery plus adjuvant RT are illustrated in Figure 3. The 10-year distant metastasis-free survival rates for surgery and adjuvant RT compared with RT alone were as follows: I–III, 77% versus 94% ($P = 0.1776$); IV, 49% versus 55% ($P = 0.5040$); and overall, 67% versus 69% ($P = 0.9764$). Multivariate analysis of distant metastasis-free survival revealed that overall stage ($P < 0.0001$) significantly influenced this end point.

Cause-Specific Survival

The cause-specific survival rates for the overall group and for the subsets of patients treated with RT alone and surgery plus adjuvant RT are shown in Figure 4. The 10-year cause-specific survival rates for surgery and adjuvant RT compared with RT alone are as follows: I–III, 77% versus 92% ($P = 0.2343$); IV, 40% versus 23% ($P = 0.4736$); and overall, 63% versus 44% ($P = 0.0243$). Multivariate analysis of cause-specific survival revealed that overall stage ($P < 0.0001$) impacted this end point.

Overall Survival

Figure 5 shows the overall survival rates for the entire group and for the subsets of patients treated with RT alone and surgery plus adjuvant RT. The 10-year overall survival rates after surgery and adjuvant RT compared with RT alone were as follows: I–III, 59% versus 65% ($P = 0.8021$); IV, 27% versus 21% ($P = 0.7605$); and overall, 48% versus 35% ($P = 0.0482$). Multivariate analysis of overall survival revealed that overall stage ($P < 0.0001$) and N classification ($P = 0.0186$) significantly influenced this end point.

Complications

Twenty-three patients (10%) developed severe complications, and 1 patient died as a result. Five patients developed severe postoperative complications includ-

ing resection and reconstruction of a necrotic tongue due to vascular compromise ($n = 1$), hemorrhage necessitating reoperation ($n = 2$), orocutaneous fistula necessitating surgery ($n = 1$), and mandibular fracture necessitating reconstruction ($n = 1$).

Four patients were hospitalized during RT for dehydration.

Thirteen patients developed severe late complications including osteoradionecrosis of the mandible necessitating surgery ($n = 3$), osteoradionecrosis of the temporal bone ($n = 1$), anticipated unilateral loss of vision ($n = 6$), orocutaneous fistula ($n = 1$), submental abscess ($n = 1$), and atypical meningioma necessitating surgery and postoperative RT ($n = 1$). Patients who developed anticipated loss of vision in the ipsilateral eye received high-dose RT to the eye to adequately treat the tumor. Thus, coding loss of vision in the treated eye is akin to coding enucleation performed as part of a cancer operation as a complication rather than part of the surgical procedure.

One patient underwent a salvage craniofacial resection and died due to postoperative meningitis.

DISCUSSION

Several questions pertain to the treatment of salivary gland carcinomas: Is adjuvant RT beneficial? What parameters influence prognosis after surgery and postoperative RT? What is the efficacy of RT alone? What is the efficacy of neutron RT?

Is Adjuvant Radiotherpay Beneficial?

It is difficult to assess the efficacy of adjuvant RT because there are no randomized data. In addition, institutional bias renders most single-institution experiences unable to address the question. For example, patients at the University of Florida are routinely presented to a multidisciplinary tumor board before treatment so that essentially all high-risk patients receive adjuvant RT. There is no high-risk group of patients treated with surgery alone with which to compare the surgery and RT group. Nevertheless, there are limited nonrandomized single-institution data that pertain.

Armstrong et al.[9] reported on 46 patients with previously untreated major salivary gland malignancies who underwent surgery and postoperative RT at the Memorial Sloan-Kettering Cancer Center (New York) between 1966 and 1982. The median RT dose was 56.6 Gy (range, 40–77.4 Gy). A matched-pair analysis was performed whereby each patient was matched with a surgery-alone control, treated between 1939 and 1965, according to site, age, histologic type, grade, and overall AJCC stage. The median follow-up period was 10.5 years after surgery alone and 5.8 years after surgery and adjuvant RT. Although the group of patients treated with surgery and adjuvant RT had improved 5-year local control and cause-specific survival rates (73% vs. 66% and 69% vs. 55%, respectively), the differences were not statistically significant. However, when stratified according to AJCC stage, patients with Stage III–IV disease benefited significantly from adjuvant RT compared with patients with Stage I–II disease. The 5-year local control and cause-specific survival rates for patients with Stage III–IV disease after surgery and RT compared with surgery alone were 51% versus 17% ($P = 0.14$) and 51% versus 10% ($P = 0.015$), respectively.

North et al.[8] reported on 87 patients with carcinoma of the major salivary gland treated at John Hopkins University (Baltimore, MD) between 1975 and 1987 with surgery alone ($n = 23$) or followed by postoperative RT ($n = 64$). Sixty-nine patients were previously untreated and 18 patients were treated for recurrent disease. Of the 23 patients treated with surgery alone, 14 (61%) had local control compared with 59 of 64 patients (92%) treated with surgery and postoperative RT. Multivariate analysis of local control revealed that facial nerve paresis ($P < 0.001$) and treatment with surgery alone ($P < 0.001$) were significantly associated with decreased local control. The 10-year cause-specific and overall survival rates were 71% and 57%, respectively. Multivariate analysis of overall survival revealed the following parameters to be associated with decreased survival: facial nerve paresis ($P < 0.001$), undifferentiated histology ($P = 0.002$), male gender ($P = 0.008$), skin involvement ($P = 0.012$), and treatment with surgery alone ($P = 0.014$). Two of 64 patients (3%) experienced RT complications. One had soft tissue necrosis that healed with conservative treatment and the other had osteoradionecrosis of the mandible that necessitated surgical intervention. The latter patient was treated with surgery and postoperative RT and subsequently underwent an iodine-125 seed implant after experiencing recurrent disease.

The limited data available support the contention that postoperative RT increases both local control and survival for patients with advanced-stage disease and/or high-grade tumors.

What Parameters Influence Prognosis after Surgery and Postoperative Radiotherapy?

Garden et al.[7] reported on 166 patients with parotid carcinomas treated with macroscopic total resection and postoperative RT at the The University if Texas M. D. Anderson Cancer Center (Houston, TX) between 1965 and 1989. Thirty-eight patients were treated for recurrent disease and 128 patients had previously untreated neoplasms. The indications for postoperative RT included inadequate margins (63%), extraglandu-

lar extension (49%), perineural invasion (34%), and/or lymph node metastases (26%). The 10-year local control rate was 90%. Multivariate analysis of local control revealed that both facial nerve sacrifice and positive lymph nodes were significantly associated with decreased local control. Histology had no impact on this end point. Ten patients (6%) experienced regional disease recurrence. Of these 10 patients, 3 also had local recurrence and 9 had high-grade tumors. The 10-year disease recurrence-free survival rate was 71%. Disease recurrence was significantly more likely to occur in patients with five or more positive lymph nodes, male gender, named nerve involvement, and extraglandular extension. Distant metastases developed in 18% of patients who had locoregional control. The 10-year overall survival rate was 60%. Multivariate analysis revealed that five or more positive lymph nodes, facial nerve sacrifice, and extraglandular extension were significantly associated with decreased survival. Significant complications included myelopathy (2%), temporal lobe necrosis (1%), soft tissue necrosis and/or bone exposure/necrosis (9%), infield second malignancies (1%), and reduced hearing (7%).

Storey et al.[5] reported on 83 patients with submandibular gland carcinomas treated with surgery and postoperative RT at the M. D. Anderson Cancer Center between 1965 and 1995. Patients had follow-up for 5 to 321 months (median, 82 months). The 10-year local–regional control and disease-free survival rates were 88% and 53%, respectively. Adenocarcinoma, high-grade histology, and treatment during the early part of the study period were associated with diminished locoregional control and disease-free survival. The 10-year overall survival rate was 55%. Eight patients (10%) experienced late complications including osteoradionecrosis (5 patients), recurrent otitis (2 patients), and perforation of the tympanic membrane (1 patient).

Le et al.[10] reported on 54 patients with minor salivary gland carcinomas treated with surgery and postoperative RT at Stanford University (Palo Alto, CA) between 1966 and 1995. The median follow-up period for living patients was 7.8 years (range, 2.1–28.9 years). The 10-year local control rate was 88%. Parameters associated with decreased local control were T3–T4 tumors, positive margins, adenocarcinoma histology, and sinonasal and oropharyngeal primary sites. The 10-year distant metastasis-free survival rate was 81%. The risk of developing distant metastasis was increased for patients with T3–T4 tumors, positive lymph nodes at diagnosis, and adenoid cystic carcinoma and high-grade mucoepidermoid carcinoma histologies. The 10-year cause-specific and overall survival rates were 81% and 63%, respectively. TN classification and overall AJCC stage significantly influenced overall survival. Three patients (6%) experienced complications including osteoradionecrosis ($n = 2$) and cataracts ($n = 1$).

Thus, the parameters associated with a poor prognosis include advanced-stage disease, incomplete resection, and high-grade histology.

What is the Efficacy of Radiotherapy Alone?

The standard of care treatment for salivary gland carcinomas is surgery alone or followed by postoperative RT. Therefore, RT alone is used primarily for patients with advanced-stage, incompletely resectable tumors and for the small subset of patients with tumors in locations where resection would result in a major functional and/or cosmetic deficit. Thus, for the most part, patients treated with RT alone have an unfavorabe prognosis. Based on our experience, approximately 20% of patients with Stage IV disease will be cured with RT alone.

What is the Efficacy of Neutron Radiotherapy?

Douglas et al.[19] reported on 279 patients treated at the University of Washington (Seattle, WA) with neutron RT with a median follow-up of 36 months (range, 1–142 months). One hundred forty-one patients had major salivary gland carcinomas, and 138 patients had minor salivary gland neoplasms. Nine percent of patients had received previous RT. The predominant histology was adenoid cystic carcinoma (68%). Macroscopic disease was present at the time of neutron RT in 263 patients (94%). The 6-year locoregional control rate was 59%. Multivariate analysis revealed that tumor size ≤ 4 cm, no base of skull invasion, previous surgical resection, and no previous RT were associated with improved locoregional control. The 6-year distant metastasis-free survival rate was 64%. Negative lymph nodes and no base of skull invasion were associated with a lower likelihood of developing distant metastases. The 6-year cause-specific survival rate was 67%. Multivariate analysis revealed that Stage I–II disease, minor salivary gland primary site, no base of skull invasion, and no previous treatment were associated with improved cause-specific survival. A moderate or severe complication developed in 17 patients (6%); no complications were fatal. Complications included osteoradionecrosis of the middle ear ($n = 1$), cervical myelopathy ($n = 1$), central nervous system necrosis ($n = 4$), optic neuropathy and blindness ($n = 3$), palatal fistula ($n = 1$), acute angle glaucoma necessitating enucleation ($n = 1$), osteoradionecrosis of the mandible or facial bones ($n = 4$), and retinopathy resulting in blindness ($n = 2$).

Laramore et al.[20] reported the results of a combined Radiation Therapy Oncology Group and Medical Research Council trial conducted between 1980

and 1986. In that study, patients with inoperable, previously untreated or recurrent major or minor salivary gland carcinomas were randomized to receive neutron RT ($n = 13$) or conventional RT ($n = 12$). Patients were stratified according to previous treatment, tumor size, and histology. The trial was stopped prematurely because patients treated with neutron RT had a more favorable outcome compared with patients who received conventional RT. The 10-year locoregional control rates after neutron RT compared with conventional RT were 56% and 17%, respectively ($P = 0.009$). In contrast, the 10-year survival rates were 15% after neutron RT compared with 25% after conventional RT ($P = 0.50$). Most of the patients treated with neutron RT had distant disease recurrence, whereas most of the conventionally treated patients experienced locoregional disease recurrence. The severe and life-threatening complication rates were 69% (9 of 13 patients) and 15% (2 of 13 patients) after neutron RT compared with 33% (4 of 12 patients) and 8% (1 of 12 patients) after conventional RT ($P = 0.07$).

The optimal treatment for salivary gland carcinoma is surgery. Postoperative RT is associated with an improved outcome for patients with advanced-stage disease, incomplete resection, and/or high-grade histology. A modest subset of patients are cured with RT alone. Neutron RT may be associated with an improved outcome for patients with macroscopic disease but probably results in a higher rate of moderate and severe complications. Adjuvant chemotherapy has no proven role in the treatment of this disease.

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