RADIOTHERAPY ALONE OR COMBINED WITH SURGERY FOR ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK

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Abstract: Background. The purpose of this study was to analyze the results of radiotherapy (RT) alone or combined with surgery for adenoid cystic carcinoma.

Methods. Between September 1966 and November 2001, 101 previously untreated patients were treated with curative intent with RT alone or combined with surgery. Follow-up ranged from 0.4 to 30.6 years (median, 6.6 years). All living patients had follow-up for at least 1 year.

Results. The 5- and 10-year rates of local control were as follows: RT alone, 56% and 43%; surgery and RT, 94% and 91%; and overall, 77% and 69%. Multivariate analysis of local control revealed that T stage (p = .0101) and treatment group (p = .0008) significantly influenced this endpoint. The 5- and 10-year rates of distant metastases-free survival were 80% and 73%. The 5- and 10-year absolute survival rates were as follows: RT alone, 57% and 42%; surgery and RT, 77% and 55%; and overall, 68% and 49%. Multivariate analysis of absolute survival revealed that T stage (p = .0043) and clinical nerve invasion (p = .0011) significantly influenced this endpoint. The 5- and 10-year cause-specific survival rates were as follows: RT alone, 65% and 48%; surgery and RT, 81% and 71%; and overall, 74% and 61%. Multivariate analysis revealed that T stage (p = .0008) and clinical nerve invasion (p = .0005) significantly influenced cause-specific survival.

Conclusions. The optimal treatment for patients with adenoid cystic carcinoma is surgery and adjuvant RT. A significant proportion of patients with incompletely resectable disease are cured after RT alone. Improvements in locoregional control are offset, in part, by the relatively high incidence of distant metastases. © 2004 Wiley Periodicals, Inc. Head Neck 26: 154–162, 2004

Keywords: carcinoma; adenoid cystic; radiotherapy; surgery
Adenoid Cystic Carcinoma of the Head and Neck

The natural history of adenoid cystic carcinoma is characterized by an indolent growth rate, a relatively low probability of regional lymph node metastases, and a high likelihood of hematogenous dissemination. The most common site of distant metastases is the lung. Adenoid cystic carcinomas may be graded histologically on the basis of the solid tumor component: grade 1, no solid component; grade 2, less than 30% solid component; and grade 3, greater than 30% solid component. Franzen et al. reported 51 patients treated at the National Hospital (Oslo, Norway) and observed that prognosis was adversely influenced by grade 3 histology (p = .0001), DNA aneuploidy, and an S phase of 6% or greater (p = .0044). Luna et al. reported a series of 26 patients with submandibular gland adenoid cystic carcinomas treated at The University of Texas M. D. Anderson Cancer Center (Houston, TX) and found that aneuploid tumors were associated with a higher likelihood of solid cytoarchitecture, lymph node metastases, and advanced stage. Norberg-Spaak et al. at the Linköping University Hospital (Linköping, Sweden) analyzed MIB-1 positivity as an indicator of proliferation in a series of 31 patients and found that the mean percent of MIB-1–positive cells significantly correlated with histologic grade: grade 1, 4.8%; grade 2, 8.0%; and grade 3, 20.2% (p = .053). The likelihood of recurrence was significantly lower for patients with low MIB-1 positivity. Spiro reported a 33% 20-year survival rate for a series of 275 patients treated at Memorial Sloan-Kettering Cancer Center; a trend toward improved survival for patients with low and intermediate grade tumors disappeared after 10 years of follow-up.

The purpose of this article is to evaluate the efficacy of radiotherapy (RT) alone or combined with surgery for patients with previously untreated adenoid cystic carcinomas of the head and neck.

METHODS

One hundred one patients with previously untreated adenoid cystic carcinomas of the head and neck received RT alone or combined with surgery at the University of Florida between September 1966 and November 2001. There were 52 males and 49 females. The ages ranged from 13.4 to 82.9 years (median, 57.7 years; mean, 56.3 years). Eighty-nine patients were Caucasian, 10 were African-American, one was Hispanic, and one was Filipino. No patients had distant metastases at presentation, and all were treated with curative intent. Patients were excluded if they had adenoid cystic carcinomas arising in the skin or the external auditory canal. Median follow-up was 6.6 years (range, 0.5 years–30.6 years). All living patients had follow-up for 1 year or more. Four patients were lost to follow-up at 8.9, 11.0, 14.2, and 21.5 years. All patients lost to follow-up were disease-free at the last follow-up and are currently alive according to the Social Security Death Index. For the purposes of data analysis, they were censored at last follow-up. The number of patients alive at various time intervals after treatment versus treatment group were: 5 years, RT alone (23 patients) and surgery plus RT (36 patients); 10 years, RT alone (15 patients) and surgery plus RT (19 patients); and 15 years, RT alone (seven patients) and surgery plus RT (eight patients), respectively. Patients were staged according to the 2002 American Joint Committee on Cancer (AJCC) staging system. Because of the relatively small number of patients, T4A and T4B lesions were grouped together (T4), as were overall stage IVA and IVB cancers (IV). Although there is no overall AJCC staging system for lacrimal gland cancers, all four patients had T4 tumors that were incompletely resectable and were classified as having stage IV disease. Thirty-two patients had clinical evidence of a cranial nerve involvement at presentation. The characteristics of the patient population are depicted in Table 1.

The treatment philosophy over the study period was to resect the primary lesion if it seemed to be completely resectable, the patient was thought to be medically operable, and the functional and cosmetic result was judged to be acceptable. Postoperative RT was recommended for essentially all patients. In the early years of the study, a small subset of patients underwent a course of preoperative RT followed by a reevaluation and surgery if the tumor response to RT was thought to be suboptimal. Three patients received preoperative RT and resection. Patients treated with RT alone were those with incompletely resectable cancers and a small subset of patients with early-stage tumors located in sites, such as the soft palate, where primary RT was recommended.

The clinically negative neck was electively dissected at the time of surgery at the discretion of...
the attending physician; nine patients received an elective neck dissection. Likewise, elective neck RT was used at the discretion of the attending radiation oncologist in patients with tumors located in primary sites thought to be relatively rich in capillary lymphatics. Fifty-five of 88 patients had an undissected clinically negative neck and received elective neck RT; the remaining patients were observed.

Four patients were initially seen with clinically positive neck nodes; three of four underwent resection of the primary tumor and a neck dissection that revealed positive node(s). All three patients received postoperative RT to the neck in addition to the primary site. One patient was treated with RT alone to a base of tongue primary lesion and a clinically positive neck; a planned postradiotherapy neck revealed residual disease in the neck that was successfully resected.

All patients were treated with megavoltage photons and/or electron beams; no patients received neutrons. Sixty-one patients were treated with once-daily fractionation, and 40 patients received twice-daily fractionation using a hyperfractionated schedule. Hyperfractionation was more likely to be used during the latter part of the study period for patients treated with RT alone to improve the likelihood of local control and/or reduce the risk of late complications, such as optic neuropathy. Ninety-two patients received continuous-course RT, and nine patients received planned split-course RT. The latter technique was used at the University of Florida between 1970 and 1974 and has since been abandoned. The initial treatment portals routinely included the path of potential perineural invasion between the primary site and the skull base. The median external beam doses for the three RT groups were as follows: RT alone, 72.4 Gy (range, 61.3 Gy–79.2 Gy); preoperative RT, 50 Gy (range, 45 Gy–61.3 Gy); and postoperative RT, 67.8 Gy (range, 10.5 Gy–76.8 Gy).

Two patients received interstitial brachytherapy as a part of their RT treatment. One patient

Table 1. Patient population (N = 101).

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Table 1. (continued)

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*Presentation with a solitary level 1 lymph node metastasis.

†Three patients who were stage N0 had a solitary positive node on elective neck dissection.
received a radium needle implant and 10.5-Gy external beam RT after a wide local excision of the primary tumor. Another patient with an oral tongue primary cancer received an iridium hairpin implant after external beam RT.

Two patients received adjuvant chemotherapy. One patient with T4N0 cancer of the tonsillar fossa received RT and four cycles of intra-arterial cisplatin (RADPLAT).17 A second patient underwent surgery for a T4N0 maxillary sinus lesion and had diffusely positive margins; he received weekly paclitaxel during a course of hyperfractionated postoperative RT.

SAS software was used to perform all statistical computations.18 The rates of local control, neck control, locoregional control, distant metastases, cause-specific survival, and survival were calculated using the product-limit method.19 The log-rank statistic was implemented to test for significant differences among these endpoints between strata of potential explanatory variables.20 Multivariate analyses were performed with Cox regression; specifically backward selection was implemented to create the most parsimonious model for each endpoint from selected explanatory variables.21 The parameters included in the various multivariate analyses included the following: primary site (major vs minor salivary gland), T stage (T0–T2 vs T3–T4), clinical N stage (N0 vs N positive), overall stage (I–III vs IV), nerve invasion (none or incidental vs clinical), treatment group (RT alone to the primary site vs RT and surgery), and elective neck RT (none vs partial or total elective neck RT vs not applicable). Not applicable includes the four patients with clinically positive neck nodes and the nine patients with clinically negative neck nodes, who underwent an elective neck dissection. Incidental perineural invasion implies nerve invasion discovered histologically without accompanying clinical symptoms. Histologic grade was not included because the philosophy of the attending pathologists was to not grade adenoid cystic carcinomas during the period of the study.

Severe complications were defined as those necessitating hospitalization, requiring surgical intervention, and/or resulting in death.22

RESULTS

Time to Recurrence. Forty-five patients had recurrent disease develop after treatment. The median time to recurrence was 2.3 years (range, 0.3 years–20.2 years). The cumulative percentage of recurrences observed at various points in time after treatment were: 5 years, 73%; 10 years, 91%; 15 years, 96%; 20 years, 98%; and 25 years, 100%.

Local Control. Local control rates at 5 and 10 years were as follows: T0–T2, 92% and 89%; T3–T4, 64% and 51%; and overall, 77% and 69% (Figure 1). The local control rates at 5 and 10 years were 56% and 43% after RT alone compared with 94% and 91% after the combination of surgery and RT. Twenty-nine of 44 patients with T4 cancers were treated with RT alone, and 15 patients received surgery and adjuvant RT. The 5- and 10-year local control rates for patients with T4 cancers were as follows: RT alone, 44% and 30%; and surgery combined with RT, 93% and 62%.

Multivariate analysis of local control revealed that T stage (p = .0101) and treatment group (p = .0008) significantly influenced this endpoint.

Neck Control. Eighty-eight patients were initially seen with a clinically negative neck; 33 were observed, and 55 received elective neck RT. The rates of neck control at 5 and 10 years were observation, 97% and 90%; elective neck RT, 98% and 98%; and overall, 97% and 95% (Figure 2). Multivariate analysis of neck control in these 88 patients revealed that none of the variables tested significantly influenced this endpoint.

Nine patients underwent an elective neck dissection; six of nine had pathologically negative neck nodes. Five of six received postoperative RT to the primary site and neck and remained disease-free in the neck. One of six patients received
postoperative RT to the primary site alone; recurrent disease developed in the neck and lungs. A salvage neck dissection was performed, and the patient subsequently died of distant metastases alone. Three (33%) of nine patients who underwent an elective neck dissection had a single positive node and received postoperative RT to the primary site and neck. All three patients remained regionally controlled.

Four patients initially had clinically positive neck nodes; all were treated with neck dissection and RT and had positive nodes on pathologic examination of the neck dissection specimen. The neck remained continuously disease-free in all four patients.

**Locoregional Control.** The locoregional control rates at 5 years versus overall stage were as follows: stage I, 89%; stage II, 85%; stage III, 93%; stage IV, 55%; and overall, 75% (Figure 3). Locoregional control at 5 years was 56% after RT alone compared with 90% after RT and surgery. Multivariate analysis of locoregional control revealed that clinical nerve invasion \( (p = .0055) \), treatment group \( (p = .0003) \), and elective neck irradiation \( (p = .0301) \) significantly influenced this endpoint.

**Distant Metastases.** The distant metastases-free survival rates were 80% at 5 years and 73% at 10 years (Figure 4), which correspond to 5- and 10-year rates of development of 20% and 27%, respectively. Multivariate analysis of distant metastases-free survival revealed that clinical evidence of perineural invasion \( (p = .0015) \) significantly impacted this endpoint. The 5-year rate of distant metastases-free survival was 61% for patients with clinical perineural invasion compared with 82% for patients with incidental nerve invasion and 92% with no clinical or pathologic evidence of nerve invasion before treatment.

**Survival.** The absolute survival rates at 5 years versus overall stage were as follows: stage I, 94%; stage II, 85%; stage III, 77%; stage IV, 45%; and overall, 68% (Figure 5). The 5- and 10-year absolute survival rates after RT alone compared with surgery and RT were as follows: stages I–III, 75% and 67% vs 90% and 63%; stage IV, 50% and 29% vs 35% and 35%; and overall, 57% and 42% vs 77% and 55%, respectively. Multivariate analysis of absolute survival revealed that T stage...
(p = .0043) and clinical perineural invasion (p = .0011) significantly influenced this endpoint.

The cause-specific survival rates at 5 years were as follows: stage I, 94%; stage II, 95%; stage III, 93%; stage IV, 49%; and overall, 74% (Figure 6). The 5- and 10-year cause-specific survival rates after RT alone compared with surgery and RT were as follows: stages I–III, 100% and 89% vs 92% and 80%; stage IV, 52% and 30% vs 44% and 44%; and overall, 65% and 48% vs 81% and 71%, respectively. Multivariate analysis of cause-specific survival rates revealed that T stage (p = .0008) and clinical perineural invasion (p = .0005) significantly influenced this endpoint.

Complications. Two patients experienced a significant postoperative complication; one patient underwent a reoperation for a postoperative hematoma, and another patient required a second surgical procedure to remove part of a necrotic tongue after a partial glossectomy. Neither patient had received RT before surgery.

Four patients experienced significant acute complications during RT. Three patients were hospitalized for nausea and dehydration. An additional patient had a submental abscess after a radium needle implant of the floor of mouth that necessitated hospitalization and drainage of the abscess.

Six patients experienced severe late complications. Three patients experienced a bone exposure and/or necrosis that required surgical intervention. One patient with a cervical esophageal primary lesion was treated with preoperative RT, esophagectomy, and gastric transposition and required a permanent jejunostomy tube because of chronic aspiration. One patient treated with surgery and postoperative RT for a lesion of the maxillary sinus developed an antral cutaneous fistula that necessitated hyperbaric oxygen treatments and a radial forearm free flap. One patient with a tracheal primary site who underwent resection and postoperative RT had tracheal stenosis develop and died of a postoperative hemorrhage after a reconstructive procedure performed 16 months after the initial tracheal resection.

One patient experienced fatal meningitis after a salvage operation performed for a locally recurrent nasal cavity tumor that had been treated with RT alone 49 months before surgery.

Six patients received high-dose RT to an ipsilateral eye and had expected visual loss in the treated eye. No patients experienced bilateral blindness.

DISCUSSION

A variety of questions are related to the treatment of patients with adenoid cystic carcinomas of the head and neck. Following is a discussion of these relevant issues.

Is Adjuvant RT Beneficial? Recent data comparing surgery alone with surgery and adjuvant RT are limited because adenoid cystic carcinomas are considered to be high-grade neoplasms and are often treated with combined-modality therapy. It has been our policy to use adjuvant RT after surgery, regardless of margin status, in essentially
all patients. The occasional patient with a grade 1 T1N0 lesion resected with widely negative margins may be observed.

Matsuba et al\textsuperscript{9} reported 76 patients treated with surgery and/or RT at Washington University (St. Louis, MO) between 1963 and 1980; 24 (32\%) of 76 patients were treated for recurrence after prior therapy. The 10-year local control rate was 83\% after surgery and RT compared with 25\% after surgery alone. Miglianico et al\textsuperscript{6} reported 102 patients treated for recurrence after prior therapy. The 10-year local control rate was 76\% after surgery and RT compared with 25\% after surgery alone. Miglianico et al\textsuperscript{6} reported 102 patients treated at the Institut Gustave Roussy (Villejuif, France) between 1951 and 1980 with surgery (38 patients), RT (21 patients), or surgery and RT (43 patients). The 5-year locoregional control rates were 44\% after surgery compared with 78\% after surgery and RT (\(p < .01\)). However, the improvement in locoregional control did not result in a significant improvement in survival rates after surgery compared with combined-modality therapy: 5-year disease-free survival, 49\% and 54\% (NS), and 5-year overall survival, 83\% and 72\% (NS), respectively. The lack of a survival advantage for those treated with surgery and RT was thought to be due to the high rate of distant metastases that was observed in 31\% of the patient population and the relatively high likelihood of long-term survival after salvage therapy for patients who had a locoregional recurrence develop (70\% survival rate 5 years after salvage treatment).

Garden et al\textsuperscript{5} reported 198 patients treated with surgery and postoperative RT at M. D. Anderson Cancer Center between 1962 and 1991; 37 (19\%) underwent surgery for recurrent disease after prior treatment. Resection margins were microscopically positive in 83 patients (42\%) and close (\(\leq 5\) mm) or equivocal in 55 patients (28\%); no patients had gross residual disease after surgery. The overall local control rates were as follows: 5 years, 95\%; 10 years, 86\%; and 15 years, 79\%. The 10-year local control rates versus margin status were as follows: microscopically positive, 77\%; close or equivocal, 92\%; and negative, 93\%. The presence of microscopically detected perineural invasion did not significantly decrease the probability of local control (\(p = .28\)), whereas invasion of a named nerve was associated with a lower probability of local control (\(p = .02\)). Patients with positive margins had an improved likelihood of local control with RT doses of 56 Gy or more, 88\% versus 40\% (\(p = .006\)). Five patients (3\%) had recurrence of the neck develop, and 74 patients (37\%) experienced distant metastases. The rates of freedom from relapse and overall survival were as follows: 5 years, 68\% and 82\%; 10 years, 52\% and 65\%; and 15 years, 45\% and 48\%, respectively.

Is RT Alone as Effective as Surgery and Adjuvant RT? Comparison of the efficacy of RT alone with that of surgery and RT is hampered by selection bias; patients with early-stage lesions that are resectable tend to undergo surgery, whereas those with advanced, unresectable cancers tend to be treated with RT alone. A subset of patients with early-stage, resectable cancers may be treated with RT alone, depending on the location of the tumor, the patients’ wishes, and the philosophy of the attending physician(s).

Matsuba et al\textsuperscript{9} observed local control in 31 (86\%) of 36 patients after surgery and RT compared with five (45\%) of 11 patients treated with RT alone. They observed improved survival in patients treated with surgery and RT compared with those treated with RT alone or combined with an incomplete resection. Cowie and Pointon\textsuperscript{1} reported 82 patients treated at the Christie Hospital and Holt Radium Institute (Manchester, UK) with either RT alone (41 patients) or RT combined with a subtotal resection (41 patients). The 5-year local control rates were as follows: 37\% after RT alone compared with 86\% after incomplete surgery and RT (\(p < .0001\)). In contrast, Miglianico et al\textsuperscript{6} reported the following 5-year outcomes in a series of patients treated with RT alone (21 patients) or surgery and RT (43 patients): locoregional control, 66\% versus 78\%; disease-free survival, 47\% versus 54\%; and survival, 79\% versus 72\%. Although there was a modest decrease in locoregional control in the group of patients treated with RT alone, it had no adverse effect on the likelihood of survival at 5 years. Our data are consistent with those reported by Miglianico et al.\textsuperscript{6} The 10-year outcomes after RT versus surgery and RT were as follows: local control, 43\% versus 91\%; absolute survival, 42\% versus 55\%; and cause-specific survival, 48\% versus 71\%.

The improvement in local control after combined-modality therapy compared with RT alone is probably due to a combination of improved efficacy and selection bias.

Is Neutron RT Preferable to Conventional Photons and/or Electrons? Neutron RT might be associated with an improved probability of locoregional control compared with conventional megavoltage photon and/or electron beams because of a lower oxygen enhancement factor (OER), less repair of sublethal damage, and less variation of radio-
sensitivity through the cell cycle. Therefore, neutrons might be preferable to treat large, slow-growing, hypoxic tumors such as advanced adenoid cystic carcinomas.

Catterall and Errington reported a series of 65 patients treated with neutron RT at the Hamersmith Hospital (London) between 1969 and 1984 for advanced salivary gland malignancies. Twenty-eight patients (43%) received prior surgery, and 14 patients (22%) had received prior RT. Twenty-five (38%) of 65 patients had adenoid cystic carcinomas; local control was achieved in 19 patients (76%). Huber et al reported 75 patients with inoperable, recurrent, and/or incompletely resected adenoid cystic carcinomas treated at the University of Heidelberg (Germany) between 1983 and 1995. Patients were treated with neutrons (29 patients), mixed neutrons and photons (21 patients), or photons (25 patients). The 5-year local control rates were 75% after neutron RT compared with 32% after photons alone or mixed with neutrons (p = .015). There was no significant difference (p > .10) in the cause-specific survival or survival rates between the two treatment groups, which the authors attributed to the high rate of distant metastases that was observed in 29 (39%) of the patients. Severe (grade 3 and 4) late toxicity was higher after neutron RT (19%) compared with mixed neutrons and photons (10%) or photons alone (4%). However, the differences in severe late toxicity were not statistically significant (p > .10).

Douglas et al reported 151 patients treated with neutron RT between 1985 and 1997 at the University of Washington (Seattle) for previously unirradiated, nonmetastatic locally advanced, and/or recurrent adenoid cystic carcinomas. All 151 patients had unresectable malignancies or gross residual disease after surgery. The 5-year outcomes were as follows: locoregional control, 57%; cause-specific survival, 77%; and survival, 72%. Multivariate analysis of locoregional control revealed that base of skull invasion (p < .01) and treatment with RT alone (p = .03) adversely influenced this endpoint. Locoregional control was 71% after subtotal resection and neutron RT compared with 43% after neutron RT alone (p = .03). Multivariate analysis of cause-specific survival revealed that base of skull invasion (p < .001), presence of lymph node metastases before RT (p < .01), treatment with RT alone (p = .03), and treatment of recurrent cancers (p = .04) adversely impacted this endpoint. Fifteen patients (10%) experienced severe grade 3 or 4 late complications. However, five of 15 severe late effects were anticipated loss of vision in a treated eye.

The data indicate that neutron RT might be more efficacious than conventional photon and/electron RT for treatment of patients with advanced, unresectable tumors. However, the 43% 5-year locoregional control rate after neutron RT alone reported by investigators at the University of Washington (arguably one of the largest neutron experiences) is similar to some of the locoregional control rates observed after conventional RT alone for unfavorable lesions. The 5- and 10-year local control rates after RT alone for 29 patients with T4 cancer treated at the University of Florida were 46% and 33%, respectively. In addition, neutron RT might result in an increased risk of severe late complications.

**Treatment of the Clinically Negative Neck.** The incidence of clinically positive neck nodes at diagnosis is relatively low. Four patients (4%) in our series initially had clinically positive nodes; an additional three of nine patients who underwent an elective neck dissection had a solitary involved neck node. Garden et al reported that 6 (3%) of 198 patients were initially seen with clinically positive neck nodes; four of six patients had pathologically positive neck nodes after a neck dissection. Forty-four patients underwent an elective neck dissection, and 16 (36%) had pathologically positive nodes. Therefore, 20 (10%) of 198 patients had pathologically positive nodes at the time of surgery and postoperative RT. Thirty-three patients with a clinically negative neck were treated at the University of Florida received no elective neck treatment; the 5- and 10-year rates of neck control were 97% and 90%, respectively.

The overall risk of failure in the neck is relatively low. However, it would seem to be prudent to electively treat the first-echelon nodes for patients with primary tumors in sites that are rich in capillary lymphatics, such as the base of tongue and nasopharynx.

**Adjuvant Chemotherapy.** Although the combination of concomitant chemotherapy and RT is more efficacious than RT alone for patients with advanced squamous cell carcinomas of the head and neck, experience with adjuvant chemotherapy for patients with adenoid cystic carcinomas is limited.

It is tempting to add adjuvant chemotherapy to RT alone or combined with surgery because of...
the high risk of hematogenous dissemination after treatment. However, there is no convincing evidence that adjuvant chemotherapy is beneficial for patients with this disease.  

Recent data indicate that a high proportion of adenoid cystic carcinomas stain positively for epidermal growth factor receptors (EGFRs) and may respond to agents that act as EGFR inhibitors. Vered and coworkers found that 23 (85%) of 27 paraffin-embedded specimens from patients with adenoid cystic carcinoma stained positively for EGFR.

**CONCLUSION**

The optimal treatment for patients with adenoid cystic carcinoma of the head and neck is postoperative RT and surgery. A significant proportion of patients with advanced, incompletely resectable cancers might be cured with RT alone. Whether neutron RT is more efficacious than conventional low linear energy transfer (LET) RT for patients with advanced disease remains unclear. Improvements in locoregional control are, in part, offset by the high risk of distant metastases. The role of adjuvant chemotherapy remains investigational.

**REFERENCES**