Postoperative Radiation Therapy for Adenoid Cystic Carcinoma

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1985年から1995年までに術後照射を行った腺様嚢胞癌患者32例の治療成績を，局所制御と生存率，形態保持および有害事象の点から，遡及的に検討した．対象の年齢は31～77歳(中央値55歳)，男女比は1対1であり，PSは0～2であった．原発巣は，頭頸部の大小唾液腺と乳腺および気管支腺であり，全例が切除標本により腺様嚢胞癌と病理学的に診断された．手術療法は，主に腫瘍摘出術であり，その切除断端は全例で陽性と診断された．術後照射は，個々の腫瘍部位と進展範囲により4-10 MV-X線と電子線を選択し，総線量60Gy(46-72Gy)を38回(25-47回)分割で，59日間(41-86日)かけて行った．観察期間の中央値は8.7年(4-13年)であった．全例の5年局所制御率は76%であり，5年無病ならびに粗生存率は68%と86%であった．5年局所制御率は，切除後微視的腫瘍残存20例において89%であり，可視的腫瘍残存12例において56%であり，また5年無病生存率は，微視的腫瘍残存群75%，可視的腫瘍残存群56%であり有意差を認めた．しかし，5年粗生存率は，微視的腫瘍残存群80%，可視的腫瘍残存群91%であり有意差を認めなかった．観察期間中にGrade 2以上の重篤な慢性有害反応を認めなかった．特に微視的腫瘍残存例においては，60Gy 40回(1.5Gy/fx)の分割照射により，良好な外観形態を保ちつつ，また有意な慢性有害反応を認めずに局所制御できた．腺様嚢胞癌に対する術後照射は，切除程度のいかんによらず，局所制御に関し有用な治療法であった．

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Introduction

The important role of postoperative radiation therapy in the local control of adenoid cystic carcinoma was established by the M. D. Anderson Cancer Center[1)-4)]. In their studies, the amount of residual tumor and the named nerve invasion were recognized as prognostic factors, and, even in patients with microscopically positive margins, a local control rate of more than 80% was reported. Although radical surgery with confirmed negative margins is still recommended by many surgical oncologists, it is important to consider the negative cosmetic effects and functional disadvantages of patients subjected to radical surgery for tumors with a long natural history. In these cases, a combination of organ-conserving surgery with local excision and postoperative radiation therapy might be more beneficial from the viewpoint of the patient's quality of life. No previously published study has evaluated the efficacy of organ-conserving treatment and its cosmetic results. In this retrospective study, we examined the usefulness of postoperative radiation therapy in adenoid cystic carcinoma after local resection, with emphasis on organ conservation.

Materials and Methods

Patients

From 1985 to 1995, we used radiation therapy to treat 39 Japanese patients suffering from adenoid cystic carcinoma. Seven of them, who received palliative radiation therapy, were excluded from this study. The remaining 32 patients underwent local resection followed by postoperative radiation therapy with curative and organ-conserving intent. None of the patients received any type of chemotherapy as a part of their initial treatment. The median age of the patients was 55 years (range: 31-77 years), and the male to female ratio was 1: 1. Performance status (PS) ranged from 0 to 2 (median: 1).

Table 1　Five-year local control rates estimated on the basis of gender, tumor extension (T/N), site of tumor, and status of residual tumors

		No. of Patients	5-year local control rates (%)	P value
Age	- 60 yo	19	77	
	61 yo -	13	77	> 0.5
Gender	Male	16	70	
	Female	16	100	> 0.5
PS	0-1	29	80	
	2	3	33	0.09
T	1	5	100	
	2	10	75	> 0.5
	3	3	100	
	4	14	66	
N	0	27	73	
	1	5	80	> 0.5
Site of Tumor	Major salivary gland	12	73	
	Minor salivary gland	17	73	
	Others	3	100	> 0.5
Site of Tumor	< 3 cm	16	81	
	> 3 cm	16	75	> 0.5
Perineural infiltration	Positive	7	75	
	Negative	17	86	> 0.5
	Unknown	8	62	
Lymph-vessel infiltration	Positive	9	70	
	Negative	13	90	> 0.5
	Unknown	10	66	
Residual Tumor	Microscopic	20	89	
	Macroscopic	12	56	0.007
Postoperative cosmetic evaluation*	Fair: Organ conserved	13	81	
	Good: Minor loss of tissues	10	77	
	Poor: Marked loss of tissues	8	45	> 0.5
Radiation Fractionation	1.5 Gy / day	22	80	
	2.0 Gy / day	10	76	0.33
Radiation Dose	- 59 Gy	3	100	
	60-69 Gy	24	82	
	70 Gy -	5	53	> 0.5

* analyzed with 31 patients with breast, head and neck presentations.

Adenoid cystic carcinoma and postoperative residual disease

Primary tumors mainly arose from the major and minor salivary glands of the head and neck: parotid gland, 7 patients; submandibular/sublingual salivary gland, 5; sinonasal cavity, 5; oral cavity, 5; larynx or hypopharynx, 3; nasopharynx, 3; acoustic external meatus, 1;mammary gland, 2, and bronchial gland, 1. The clinical stage of each tumor was determined using computed tomography of the primary site, chest X-rays, ultrasonography of cervical lymph nodes and upper abdomen, and bone scintigraphy. Postoperative pathological examinations showed that the maximum diameter of the tumor on the resected specimen ranged from 1.5 cm to 8.7 cm, with a median of 3.7 cm. According to the Union Internationale Contre de Cancer (UICC) system (1997), 15 patients had Stage I or II disease and 17 had locally advanced Stage III or IV disease without any distant metastases.

In 20 of the 32 patients, microscopically positive margins were found on all resected specimens. In the other 12 patients, macroscopically residual disease was documented pathologically and radiologically after surgery. Microscopic perineural infiltrations were diagnosed pathologically in 7 of 32 resected specimens, and lymph-vessel infiltrations were pathologically documented in 9 of 32 patients (Table 1).

Postoperative radiation therapy

Radiation therapy was carried out according to different techniques appropriate for the site and extension of each tumor. The radiation field of head and neck tumors included the primary site, the cervical lymph node area, and the cranial nerve pathways to the base of the skull. Radiation fields in the case

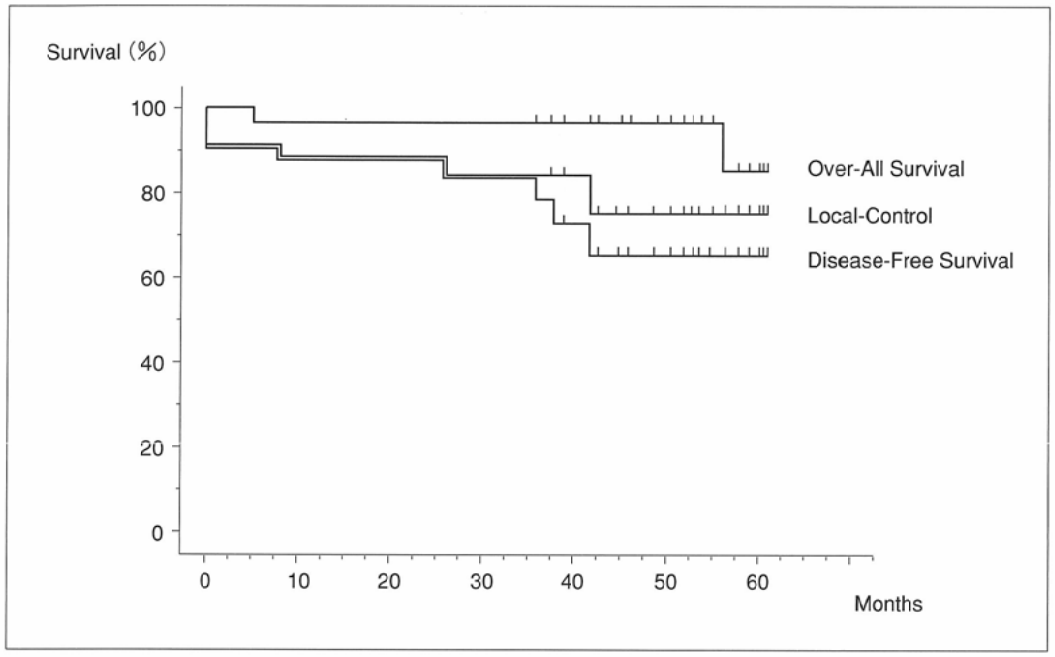

Fig. 1 Local control rate, disease-free, and overall survival curves for patients with adenoid cystic carcinoma.

of tumors arising from the breast and bronchi were the opposing breast tangential field and the opposing antero-posterior whole mediastinal field, respectively. A median dose of 60 Gy (range 46-72 Gy) was delivered in 38 fractions (range 25-47) over 59 days (range 41-86) using 4-10 MV photon beams with or without 9-15 electron beam boosts. Twenty-two of 32 patients were treated with radiotherapy using a smaller fraction size, delivering 60 Gy in 40 fractions at 1.5 Gy per day over 8 weeks. The other 10 patients were treated using radiotherapy to a median dose of 60 Gy (range 46-72 Gy) with 2 Gy daily.

Evaluation of cosmetic results and adverse effects

The status of conserved organs with minimal loss of normal tissue was defined as good, that with minor loss of normal tissue was evaluated as fair, and the status of marked loss of normal tissue owing to the surgical procedure was considered poor. Using the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity score and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity score, the adverse acute and late radiation-related effects of skin and mucous membranes were also examined[5].

Follow-up and statistical analysis

The period of observation from the end of radiation therapy ranged from 6 months to 13 years (median 8.7 years). Rates of local control, overall survival, and disease-free survival were determined using the Kaplan-Meier method. Differences regarding local control rates and survival rates according to the previously reported prognostic factors [age, gender, performance status, tumor extension (T/N), site of tumor, size of primary lesion (< 3 cm/ 3cm +), pathological findings (perineural infiltration and lymph-vessel infiltration), amount of residual disease, fraction size of irradiation, radiation dose, and postoperative cosmetic results] were tested for statistical significance using the Mantel-Cox method[2),4),6)–10)].

RESULTS

Local control and survival

The 5-year local control, disease-free, and overall survival rates for all patients were 76 %, 68 %, and 86 %, respectively (Fig. 1). The 5-year local control rate for patients with microscopically positive margins (89 %) was higher than that for patients with macroscopically residual disease (56 %) ($p = 0.007$) (Table 1). The 5-year disease-free survival rate for patients with microscopically positive margins (75 %) was higher than that for patients with macroscopically residual disease (56 %) ($p = 0.03$) (Table 2), although no significant difference in the 5-year overall survival rate was observed between them (80 % in patients with microscopically positive margins vs. 91 % in macroscopically residual disease, $p = 0.79$). An excellent 5-year local control rate (100 %) was attained in 15 patients with microscopically positive margins who were treated with radiotherapy using a smaller fraction size delivering 60 Gy in 40 fractions at 1.5 Gy per day over 8 weeks of the other 7 patients with macroscopically residual disease treated with 1.5 Gy daily, 2 were locally controlled, 3 uncontrolled, and 2 recurred locally. For the other 10 patients treated with 2 Gy daily, the 5-year local control rate

Table 2　Five-year disease-free survival rates and overall survival rates estimated on the basis of gender, tumor extension (T/N), site of tumor, and the status of residual tumors

		No. of Patients	Disease-FreeSurvival Rate (%)	P value	Over-All Survival Rate (%)	P value
Age	- 60 yo	19	71		100	
	61 yo -	13	58	0.33	76	> 0.5
Gender	Male	16	70		75	
	Female	16	100	> 0.5	100	> 0.5
PS	0-1	29	71		91	
	2	3	33	0.22	67	> 0.5
T	1	5	100		100	
	2	10	75		67	
	3	3	33	> 0.5	100	> 0.5
	4	14	66		93	
N	0	27	63		83	
	1	5	80	> 0.5	100	> 0.5
Site of Tumor	Major salivary gland	12	61		80	
	Minor salivary gland	17	61		94	
	Others	3	100	> 0.5	100	> 0.5
Residual Tumor	Microscopic	20	75		80	
	Macroscopic	12	56	0.03	91	0.79
Radiation Fractionation	1.5 Gy / day	22	80		80	
	2.0 Gy / day	10	60	0.12	96	0.85
Radiation Dose	- 59 Gy	3	100		100	
	60-69 Gy	24	67		96	
	70 Gy -	5	53	> 0.5	67	> 0.5

was 76 %.

No significant differences in the 5-year local control rate, 5-year disease-free rate, or overall survival rate were observed on the basis of gender, tumor extension (T/N, UICC), size of primary lesion, site of tumor, pathological findings (perineural infiltration and lymph-vessel infiltration), or radiation dose (Tables 1 and 2).

Adverse effects

The acute radiation-induced adverse effects that scored less than grade 2 were acceptable to all patients. No late radiation-induced adverse effects scoring more than grade 3 were observed (Table 3). Notably, no late radiation-induced adverse effects scoring more than grade 2 were observed in the patients treated with 1.5 Gy per fraction during the same period.

Cosmetic results

The postoperative cosmetic results for 29 patients with head and neck lesions were evaluated. These results were affected by the surgical procedure and tumor size. Good status was observed in 9 patients who had mostly T1 or T2 lesions. Fair status was found in 10 patients, and poor status was found in 8 patients with locally advanced cancers. No difference in cosmetic results was documented between the postoperative setting and status after postoperative radiotherapy. No significant differences in cosmetic results were observed according to radiation dose. Two patients with primary breast lesions had excellent cosmetic results.

Discussion

Role of postoperative radiation therapy and prognostic factors

The efficacy of postoperative radiation therapy was first demonstrated by Fletcher and his colleagues in 1975[1]. Excellent actuarial local control rates for patients with adenoid cystic carcinomas treated with surgery and postoperative radiation therapy were reported during the 1980s[4),6)-10)] (Table 4). According to these reports, treatment strategy is determined for each patient based on prognostic factors such as age, PS, tumor extension, size of primary tumor, positive margins, nerve involvement, and social background[1),3),4)]. Our data showed that the amount of residual tumor is also a meaningful prognostic factor. Although postoperative microscopically positive margins were found in patients after local resection with organ-conserving intent in our study, a high local control rate was achieved by postoperative radiotherapy. Therefore, it follows that head and neck surgeons resect tumors as completely as possible while removing as little normal tissue as possible. Cosmetic results were good in patients with T1-2 lesions, whereas unsatisfying results were docu-

Table 3 Adverse effects of postoperative radiation therapy according to acute (RTOG) and late (RTOG/EORTC) radiation morbidity scales

	Site	Grade	Smaller Fraction (1.5 Gy/fx)	Conventional Fraction (2.0 Gy/fx)
Acute adverse effects (RTOG)	Skin	0		
		1	20/22	6/10
		2	2/22	3/10
		3		1/10
		4		
	Mucous meambranes	0		
		1	15/18	2/9
		2	3/18	5/9
		3	1/18	2/9
		4		
Late adverse effects > 24 months (RTOG/EORTC)	Skin	0		
		1	20/21	6/10
		2	1/21	4/10
		3		
		4		
	Mucous membranes	0		
		1	15/17	6/9
		2	2/17	2/9
		3		1/9
		4		

RTOG: Radiation Therapy Oncology Group
EORTC: European Organization for Research and Treatment of Cancer

mented in some patients with advanced cancer owing to the intense surgical procedures.

Local control

Standard postoperative radiation treatment fields include areas at risk of local recurrence, that is, each primary site, cervical lymph nodes, and the cranial nerve pathways to the base of the skull[2),6)–10)]. However, the dose and fractionation schedule of postoperative radiation therapy for patients suffering from adenoid cystic carcinoma, who are expected to survive for a long time, has not as yet been established. In order to improve the efficacy of radiation therapy for locoregional control and to reduce adverse late radiation-induced effects, the slow cell cycle and long-doubling time of this slowly growing epithelial tumor are taken into account when deciding the dose to be administered and fractionation schedule[11),12)]. As a basic guideline for postoperative radiation therapy, Garden and colleagues recommended a minimum of 56 Gy to the operative bed and 60 Gy to the original tumor volume, especially when there were positive margins and/or named nerve invasion[3),4)]. A recommended dose of 66 Gy was reported to be necessary for macroscopically residual disease, i. e., multiple positive margins and extensive soft tissue involvement[4)]. Based on our 5-year local control rate of 100 %, we think that it might be possible to obtain complete tumor eradication with smaller fractionated radiotherapy using 60 Gy divided into 40 fractions over 8 weeks without any late toxicity, in the case of small amounts of residual tumor cells in microscopically positive margins. The duration of treatment, that is, 8 weeks, might be beneficial for this slowly progressive tumor. The lower local control rate obtained with a daily dose of 1.5 Gy in the case of macroscopic residual tumor indicates that it is impossible to eradicate large numbers of tumor cells with a daily dose lower than 2.0 Gy, even if we irradiate to the dose of 60 Gy. The conventional 2.0 Gy per fraction schedule and total dose higher than 60 Gy is recommended to attain good local control in patients with macroscopic residual tumors.

Chronic radiation-induced adverse effects

Because of the invasive characteristics of adenoid cystic carcinomas arising from major or minor salivary glands, external and/or middle ears, eyes, visual pathways and brain stem occasionally are unavoidably within the radiation field. In addition, more than 100 cm^2 of cutaneous tissue is frequently included within the radiation field. The chronic TD5/5 (the 5% probability of complication within 5 years) for external and/or middle ears (chronic serous otitis), for cutaneous tissue (if the field is over 100 cm^2, ulceration), and for brain stem and visual pathways (necrosis) are estimated to 55 Gy[13)]. Based on data from 224 patients with minor salivary carcinoma treated at the M. D. Anderson Cancer Center, common radiation-

Table 4　Retrospective studies on postoperative radiation therapy in adenoid cystic carcinoma

Ref. Author (Institute, year)	No. of patients / all patients	Postoperative radiation (Gy / fx. / wks)	Local control rate (years)	Disease free survival (years)	Overall survival rate % (years)	Poor Prognostic factors
6) Black et al. (* PMH, 1980)	35/62	50/20-25/4-5	29/35 (5-20)	23/35 (5-20)	57% (5-20)	
7) Cowie et al. (Christie, 1984)	41/113	50-55/15-16/3	35/41 (5)	NA	75% (5)	
8) Simpson et al. (Washington, 1984)	28/71	60/NA/NA	80% (10)	NA	60-40% (5-10)	Tumor diameter > 3 cm
9) Vikram et al. († MSKCC, 1984)	25/74	24-70/NA/NA	13/25 (5)	52% (5)	NA	Minor salivary gland (vs major salivary gland)
10) Miglianico et al. (‡IGR, 1987)	43/102	50-65/NA/NA	77.8% (5)	54.3% (5)	71.5% (5)	Bone involvement
4) Garden et al. (§ MDACC, 1995)	198	50-69/30/3-8	175/198 95-86-79% (5-10-15)	111/198 68-52-45% (5-10-15)	82-65-48% (5-10-15)	Positive margins, Named nerve invasion
This study	32	50-72/25-36/6-12	76% (5)	68% (5)	86% (5)	Amount of residual rumor

* PMH: Princess Margaret Hospital
† MSKCC: Memorial Sloan-Kettering Cancer Center
‡ IGR: Institute Gustave Roussy
§ MDACC: M.D. Anderson Cancer Center

induced complications were decreased hearing due to chronic serous otitis media (11.6%, 26/224) and visual problems (7.6 %, 17/224)[3]. Radiation-induced visual impairment was reported in 17% of patients receiving 42-55 Gy to the corneal-lacrimal apparatus[14]. Other radiation-induced adverse effects were reported in 2.8% of patients receiving 57.6 Gy in 32 fractions to the head and neck organs[15]. Based on these data, Garden and colleagues recommended the carefully designed radiation therapy of 56 Gy assured by excellent dosimetry for patients with long life expectancy[3),4)]. They also recommended treating the nerve pathways to the base of the skull only if there is named nerve invasion[3),4)]. According to the linear-quadratic model, 60 Gy in 40 fractions over 8 weeks for spinal cord and optic tracts (when the α/β ratio is estimated as 3) has the same value (TDF: 100. 2) as 46 Gy in 23 fractions over 4.6 week and is considered to be lower than the maximum neurological tolerable dose of 54 Gy in 27 fractions over 5.4 weeks[16),17)]. 60 Gy in 40 fractions over 8 weeks for cutaneous tissue (when the α/β ratio is estimated as 10) has the same value (TDF: 85.6) as 52 Gy in 26 fractions over 5.2 weeks[16),17)]. In this study, the incidence and degree of acute and late toxicity on skin and mucous membranes of the patients treated with 1.5 Gy per fraction were less than those of patients irradiated with 2.0 Gy per fraction. Smaller fraction size has less influence on the chronic radiation-induced adverse reactions of late-responding normal tissue[16)]. Considering the disadvantage of longer treatment time, such as 1 week or 2 weeks more, we would prefer to treat patients suffering from adenoid cystic carcinomas who are expected to be alive for more than 10 years with the less toxic radiation therapy using smaller fractions.

Cosmetic results

From the viewpoint of cosmetic results, the combination of local resection with organ-conserving intent and postoperative radiation therapy is effective in patients with adenoid cystic carcinoma lesions of T1/2. Our data indicate that the cosmetic results were mainly affected by tumor extension and surgical resection, and postoperative radiotherapy had no influence on the cosmetic results. For patients with T1 or T2 lesions, the combination of local resection with organ-conserving intent followed by postoperative radiation therapy provided good cosmetic results. We think that the combined treatment of more intensive surgical resection and postoperative radiation therapy should be recommended for patients with T3 or T4 lesions, because of the poor cosmetic results and low disease free-rates.

Conclusion

Postoperative radiation therapy with smaller fractions is useful, since good local control might be achieved in patients with adenoid cystic carcinoma with microscopically positive margins without inducing any adverse late reactions. However, the number of our patients was too small and our follow-up period too short to obtain a definite conclusion on fraction size. Longer studies with more patients are required to determine precisely ideal treatment intensities and lengths. We consider that further clinical trials of organ-conserving treatment using local resection and postoperative radiation therapy will be able to be conducted in patients with T1 or T2 lesions, who have negative or microscopically positive margins and are expected to be followed up for longer than 10 years or more.

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