

Results of radical radiotherapy for squamous cell carcinoma of the eyelid

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(Received 7 December 2012; revised 19 April 2013; accepted 20 April 2013)

Purpose: To analyze the results of radical radiotherapy by electron beams for squamous cell carcinoma (SCC) of the eyelid and to find the possible prognostic factors. **Materials and Methods:** Records of 38 patients with histologically confirmed SCC of the eyelid who underwent electron beam radiation therapy between 1964 and 2010 in our institution were retrospectively reviewed. Median tumor size was 15 mm (range, 3–40 mm). T stage was T1 in three, T2a in six, T2b in 14, and T3a in 15 patients. Four patients had nodal metastasis. Of the 38 patients, 14 had relapsed disease after prior treatment. Median radiation dose was 60.0 Gy (range, 45.0–70.4 Gy). Median follow-up was 72.5 months (range, 2.0–369 months). **Results:** 5-year local relapse-free, nodal relapse-free, distant metastasis-free and relapse-free rates for all patients were 71.8%, 77.5%, 90.6% and 58.0%, respectively. In seven patients, lymph node metastases occurred in 11 faciocervical regions. The 5-year overall survival was 79.5%. T stage and radiation dose expressed in EQD₂Gy tended to have impacts on local control. Relapsed patients showed unfavorable local relapse-free rate, however this was without statistical significance. Of the 14 patients who died, 12 succumbed to concurrent diseases. Grade 3 or greater severe late morbidities (CTCAE ver4.0) were observed in nine patients. Due to the morbidities, two patients lost their vision. **Conclusion:** Radical radiotherapy for SCC of the eyelid yielded good results and could be a treatment option. Whether radiation-dose escalation could improve local control in advanced T stages and relapsed patients needs further study.

Keywords: electron therapy; eyelid SCC; radiotherapy

INTRODUCTION

In western countries, eyelid carcinoma is an unusual tumor. Squamous cell carcinoma (SCC) accounts for 5–10% of all eyelid malignancies with an incidence of 0.09–2.42 per 100 000 and is the second most common malignancy of the eyelid after basal cell carcinoma (BCC) [1–7]. On the contrary, in Japan the incidence of BCC is lower and that of sebaceous carcinoma is higher, resulting in nearly the same incidence for these three types of cancers [8]. Although the absolute incidence of eyelid cancers in Japan has not been reported, they are rarely encountered in the clinical practice. Due to the rarity of eyelid carcinomas, many studies have

reported these three tumors together, despite their different clinical behaviors. SCC is aggressive tumor with a tendency for local invasion and a potential for metastasis to regional lymph nodes and distant organs.

Radical surgical excision with a frozen section control by either a standard method or Moh's micrographic surgery is the most commonly employed method of treating SCC of the eyelid. However, due to advanced age, the presence of coexisting diseases, and patient refusal, some patients are unsuitable for surgical management. Furthermore, despite recent progress in reconstructive surgery, eyelid tumor is difficult to excise completely without functional and cosmetic impairment [9, 10]. Therefore, radical radiotherapy might be a

treatment alternative for the patients who refuse surgery or who are not suitable for invasive procedures. However, limited information is currently available on the role of radical radiotherapy in the management of SCC of the eyelid.

This retrospective study was conducted to analyze the efficacy and adverse events of radical radiotherapy by electron beams for SCC of the eyelid, and to find the possible prognostic factors.

MATERIALS AND METHODS

A review of medical records of the Department of Radiation Oncology, National Cancer Center Hospital of Japan from 1964 to 2010 found 38 patients of SCC of the eyelid treated with a radical radiotherapy by electron beams. All 38 patients were inappropriate for surgery because of patient refusal or functional and cosmetic problems. Two patients were excluded; one was treated by orthovoltage X-rays, and the other underwent 4-MV X-ray irradiation for a far-advanced lesion. This study was conducted over a long period, but radiotherapy by electron beams was simple and the treatment method did not alter. Patient characteristics are shown in Table 1. The median age was 64 years (range, 39–96 years). Of the 38 patients, 16 were male and 22 were female. All 38 had ECOG performance status of 0 or 1. The right eyelid was affected in 19 patients and the left eyelid in the other 19 patients. The upper eyelid was involved most frequently (in 20 patients), while lateral canthus involvement was only seen in one patient. The median tumor size was 15 mm (range, 3–40 mm). TMN staging by the Union Internationale Contre le Cancer (UICC) [11] was used in the current study. T1 is defined by the tumor being 5 mm or less in greatest dimension, not invading the tarsal plate or eyelid margin; T2a is defined by the tumor being more than 5 mm, but not more than 10 mm in greatest dimension, or any tumor that invades the tarsal plate or eyelid margin; T2b is defined by the tumor being more than 10 mm, but not more than 20 mm in greatest dimension, or involving the full thickness of the eyelid; T3a is defined by the tumor being more than 20 mm in greatest dimension, or any tumor that invades adjacent ocular or orbital structures, or any tumor with perineural invasion; T3b is defined by the tumor whose complete resection requires enucleation, exenteration, or bone resection; T4 is defined by the tumor not being resectable due to extensive invasion of ocular, orbital, craniofacial structures, or brain. Three patients were classified as T1, six as T2a, 14 as T2b, and 15 as T3a. Four patients had lymph-node metastasis. The parotid gland lymph node was involved in one patient, the preauricular in two, and the upper cervical in one. All the four patients had T2b primaries. In 24 patients, preceding treatment had not been performed, whereas 14 patients had had a prior treatment with relapsed lesions undergoing definitive radiation therapy. In the prior treatment group, T stage and N stage was allocated to the relapsed lesions just

before the radiation therapy. Prior treatments were surgery in 10 patients, surgery and radiotherapy in two patients, radiotherapy in one patient, and laser treatment in one patient. Two of three patients did not have details about any prior radiotherapy and were treated using electron beams of 57.4 Gy and 60 Gy. The other patient had prior radiotherapy by orthovoltage X-rays of 2000 rad and was treated using electron beams of 59.4 Gy.

All 38 patients were treated with radical radiotherapy with electron beams. Two of the 24 patients without preceding treatment underwent postoperative radiotherapy for residual tumor after surgery. A direct appositional field of electron beams was used with a margin of 1–2 cm. The electron beam energy is shown in Table 2, and was selected to encompass the tumor depth by at least 90% of the axis peak dose. According to the tumor reduction, the electron beam energy was changed to lower one in nine patients. In 10 patients, a bolus was used to increase the dose to the eyelid surface (Table 2). Of the 38 patients, 34 were treated with a handmade lead block inserted under the eyelid to prevent lens exposure. A handmade lead block had enough thickness to block electron completely (Fig. 1). The median radiation dose was 60.0 Gy (range, 45.0–70.4 Gy, 2 Gy per fraction to 5 Gy per fraction). Because various fractionations were employed, the equivalent dose in 2 Gy fractions (EQD_2 Gy) was calculated using the LQ model with α/β assumed to be 10 Gy for tumor control [12].

Two of four patients with initially positive lymph nodes were treated with neck dissection, and the remaining two were treated with radiotherapy to the involved lymph nodes. No prophylactic radiation therapy to the neck was performed.

The median follow-up was 72.5 months (range, 2.0–369 months). The local relapse-free rate (LRFR), nodal relapse-free rate (NRFR), distant metastasis-free rate (DMFR), and overall survival (OS) were calculated with the Kaplan–Meier method from the start of radiotherapy using JMP[®] 9 (SAS Institute Inc., Cary, NC, USA). LRFR was defined by absence of any failure in the eyelid as an event, with death and lost to follow-up considered as censored. NRFR and DMFR were calculated similarly with absence of faciocervical nodal relapse and distant metastasis as events, respectively; again censoring was done only in the event of death or lost to follow-up. Additionally, we performed univariate analysis to find possible prognostic factors for LRFR and OS. Late morbidities were classified according to CTCAE version 4.0.

RESULTS

The site of relapse was local in 10 patients, the cervical lymph nodes in seven, and distant organs in three (Fig. 2). Five-year LRFR, NRFR, DMFR and OS were 71.8%, 77.5%, 90.6% and 79.5%, respectively (Fig. 3). Of the 38

Table 1. Patients' characteristics and clinical results (5 year LRFR, OS)

| | <i>n</i> | 5-year LRFR | <i>P</i> | 5-year OS | <i>P</i> | | |
|--------------------------------|----------|-------------|-------------------|-----------|-----------------|-------|-------|
| Whole | 38 | 71.8% | | 79.5% | | | |
| Age (median 64 years) | | | | | | | |
| age < 65 | 19 | 66.6% |] 0.662 | 75.1% |] 0.235 | | |
| age ≥ 65 | 19 | 76.7% | | 83.5% | | | |
| Sex | | | | | | | |
| male | 16 | 62.8% |] 0.393 | 66.6% |] 0.0668 | | |
| female | 22 | 77.0% | | 89.5% | | | |
| Laterality | | | | | | | |
| rt | 19 | 56.8% |] 0.0329* | 93.8% |] 0.296 | | |
| lt | 19 | 88.2% | | 66.6% | | | |
| Site | | | | | | | |
| upper eyelid | 20 | 84.4% |] 84.4%] 0.0931 | 84.4% |] 84.4%] 0.963 | | |
| lower eyelid | 12 | 53.0% | | 62.9% | | | |
| medial canthus | 5 | 60.0% | | 57.5% | | 100% | 73.6% |
| lateral canthus | 1 | NA | | NA | | | |
| T stage | | | | | | | |
| T1 | 3 | 100% |] 85.7%] 0.0281* | 100% |] 81.7%] 0.274 | | |
| T2 | 20 | 83.3% | | 78.8% | | | |
| T3 | 15 | 51.4% | | 51.4% | | 74.0% | 74.0% |
| Tumor size (median 15mm) | | | | | | | |
| 15mm < | 17 | 80.5% |] 0.27 | 87.8% |] 0.0267* | | |
| 15mm ≥ | 21 | 65.0% | | 72.0% | | | |
| N stage | | | | | | | |
| N0 | 34 | 69.3% |] 0.309 | 86.6% |] 0.0001* | | |
| N1 | 4 | 100% | | 25.0% | | | |
| Prior treatment | | | | | | | |
| yes | 14 | 52.8% |] 0.0798 | 71.4% |] 0.755 | | |
| no | 24 | 82.8% | | 84.9% | | | |
| Radiation dose | | | | | | | |
| 56 Gy < in EQD ₂ Gy | 6 | 40.0% |] 0.0524 | 75.0% |] 0.669 | | |
| 56 Gy ≥ in EQD ₂ Gy | 32 | 77.4% | | 83.3% | | | |

LRFR = local relapse-free rate, OS = overall survival, log rank test, **P* < 0.05.

patients, 14 died. Tumor-related death was seen in only two patients (5.26%), and 12 patients (31.6%) died of other causes. The median time to local relapse from radiation therapy was 13.0 months (range, 2.3–43.0 months). In 10 locally relapsed patients, eight underwent salvage surgery and one was treated by cryotherapy. In those nine patients local relapse was able to be controlled. The remaining patient underwent re-irradiation with a failure to control the relapse.

Three of the 10 patients underwent a mutilating orbital exenteration.

Of four patients with initial lymph-node metastasis, one patient who was treated with surgery relapsed in the preauricular region, while the neck of the other three patients remained controlled. In the seven patients who relapsed in the neck lymph nodes, lymph-node metastases were seen in 11 regions (parotid-gland lymph node: four, preauricular:

three, upper cervical: one, middle cervical: one, posterior cervical: one, submandibular: one). Their initial T stage was T1 in one patient out of three, T2b in four out of 14, and T3a

Table 2. Electron energy and bolus

| Electron Energy (megavoltage) | n (with bolus) |
|-------------------------------|----------------|
| 3 | 9 (0) |
| 4 | 5 (1) |
| 5 | 1 (0) |
| 5 → 3 | 2 (0) |
| 6 | 12 (4) |
| 6 → 3 | 1 (0) |
| 6 → 4 | 2 (2) |
| 9 | 2 (1) |
| 9 → 6 | 4 (2) |



Fig. 1. Examples of lead blocks with various thicknesses and sizes to protect the lens.

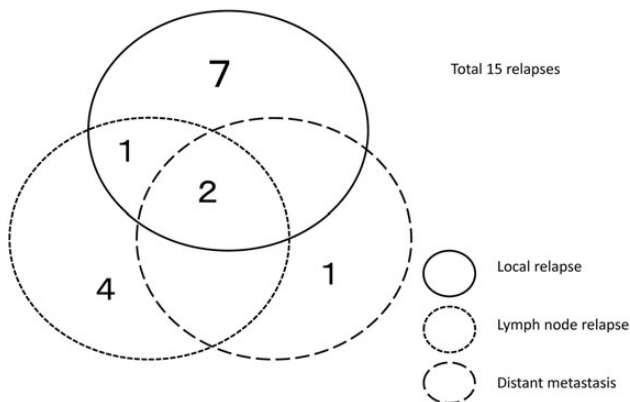


Fig. 2. Number of local, nodal and distant relapses.

in two out of 15. With advanced T stages, a tendency for lymph-node metastasis seems to be increased. As a salvage therapy for neck node relapse, four patients underwent surgery only, and two were treated with radiotherapy only. The other patient underwent surgery followed by adjuvant radiotherapy due to multiple lymph-node metastases. Salvage treatment of lymph-node relapse resulted in two re-relapses in the neck, while the neck remained controlled in the remaining five patients.

Distant metastasis was observed in three patients. One patient had lung, bone and subcutaneous metastases, and was alive with disease two years after the diagnosis of distant metastases. One patient died of lung and bone marrow metastases. One patient had lung metastasis and died of cardiac disease.

Regarding LRFR, both T stage and right-or-left side had a significant impact, with T1/T2 and a left-side tumor showing a favorable LRFR (Fig. 4). The five-year LRFRs for T1/T2 and T3 were 85.7% and 51.4%, respectively ($P=0.0281$), and those for left and right side tumors were 88.2% and 56.8%, respectively ($P=0.0329$). EQD₂ Gy had an almost statistically significant impact upon LRFR with EQD₂ Gy ≥ 56 Gy and < 56 Gy showing 5-year LRFRs of 77.4% and 40.0%, respectively ($P=0.0524$). Additionally, upper eyelid tumors had a trend towards better LRFR ($P=0.0931$). Although a statistically significant difference was not reached ($P=0.0798$), the no-prior-treatment group attained a favorable 5-year LRFR of 82.8%, while that of the relapsed group was 52.8%. One of three patients with prior radiotherapy had relapsed local, regional lymph node and distant organ, and succumbed to the disease. The other two patients had severe late adverse events of cataract and keratitis.

Grade 3 or more severe late morbidities were observed in nine patients with 12 events (Table 3). The initial tumor site was the lower eyelid in three patients, the upper eyelid in three, and the medial canthus in three. Cataract was seen in six patients, keratitis in three, and entropion, glaucoma, and contralateral sympathetic ophthalmitis in one patient each. Two patients lost their vision due to keratitis. Five of the six patients with cataract were operated on and visual acuity was restored. In the remaining patient, visual acuity was not recovered because of the concurrent occurrence of Grade 4 keratitis. One patient with Grade 4 keratitis also lost her vision.

DISCUSSION

There have been some reports about the results of radiotherapy for eyelid cancers (Table 4) [4, 5, 13, 14]. The LRFR and the relapse-free rate (RFR) have been reported as around 90% and 70%. The results are so varied due to the various stages and histologies in the study populations that it is difficult to compare the current study results with the past studies. The results of our study revealed a 5-year

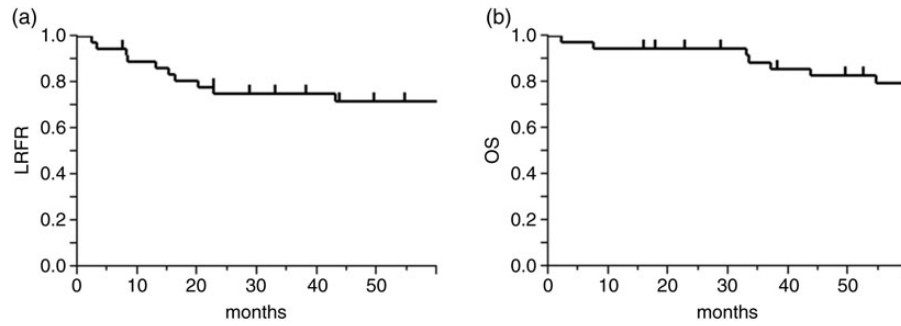


Fig. 3. LRFR and OS (a, b).

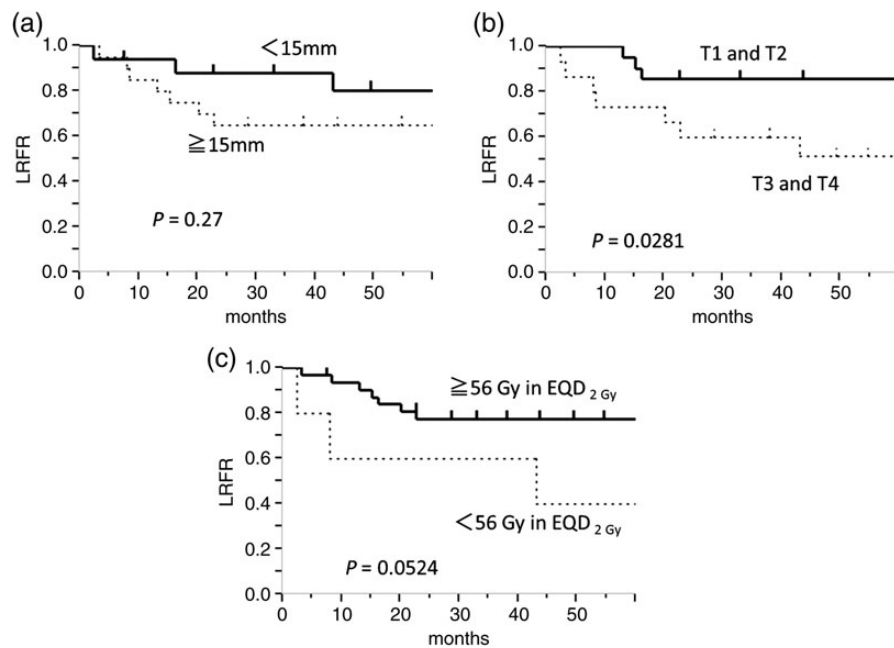


Fig. 4. LRFR by tumor size (a), T stage (b) and EQD_{2 Gy} (c).

LRFR and RFR of 71.8% and 58.0%, and this seems to be not inferior to other reports, considering that our patient population included more unfavorable patients with 14 locally relapsed patients (36.8%) and 15 T3 patients (39.5%).

Regarding prognostic factors for LRFR, left-or-right side and T stage were both statistically significant factors. The left-side tumors had a better LRFS than the right-side, because of the left eyelid tumors, 31.6% were T3, whereas 47.4% of the right eyelid tumors were T3. Similarly, upper eyelid tumor had a better LRFR because 25.0% of the upper eyelid tumors were T3, whereas 55.6% of other subsites were T3. By using EQD_{2 Gy}, there was a tendency towards a favorable LRFR in the patients treated with ≥ 56 Gy ($P = 0.0524$). Accordingly, at least ≥ 56 Gy in EQD_{2 Gy} seems to be the preferred dose to control the tumor. In our institute, 60 Gy in 30 fractions has become a practical standard.

Table 3. Grade 3 or more severe adverse events

| Adverse event | ≥Grade 3 |
|--------------------------|----------|
| Cataract | 6 |
| Keratitis | 3 |
| Glaucoma | 1 |
| Sympathetic ophthalmitis | 1 |
| Entropion | 1 |

Locally relapsed patients showed a tendency towards unfavorable LRFR. Whether dose escalation is beneficial for the advanced stages of T3 and T4 or locally relapsed patients needs further investigation.

The median time to local relapse from treatment was 13.0 months, with a range of 2.3–43.0 months. Of the local

Table 4. Past reports and their clinical results

| Author (year) | n | Size or Stage | Histology | Results | Complications |
|------------------------|------|---------------|--|--|--|
| Fitzpatrick (1984) [5] | 1166 | NA | BCC (n = 1062) SCC (n = 104) | 5-year LC 93.3% for SCC | 9.6% |
| Lederman (1976) [4] | 59 | NA | SCC | 5-year OS 67% one-year RFR 87.5% | 16.9% |
| Schlienger (1996) [13] | 850 | ≤2cm 78% | BCC (n = 694) SCC (n = 41) other (n = 115) | 5-year OS 74% 5-year RFR 72% 5-year CSD 0.5% | cataract 2% keratitis 2.4% glaucoma 0.12% vitreous hemorrhage 0.12% loss of eye 1.18% |
| Petsuksiri(2007) [14] | 39 | Median 1.4 cm | SCC | 5-year OS 71% 5-year RFR 86% | No grade 3/4 |
| Current study | 38 | T3/4: 39.5% | SCC | 5-year LC 71.8% 5-year RFR 58% 5-year OS 79.5% | keratitis 7.9% cataract 15.8% glaucoma 2.6% entropion 2.6% sympathetic ophthalmitis 2.6% |

LC = local control, SCC = squamous cell carcinoma, OS = overall survival, RFR = relapse free rate, CSD = cause specific death, NA = not available.

relapses, 90% occurred within 24 months. Close follow-up of the local control is mandatory, because salvage therapy for local relapse, especially surgery with a sacrifice of function and cosmesis, turned out to be quite effective. The effective salvage meant that T stage, which was a significant factor in LRFR, was not a statistically significant factor for OS. Locally relapsed patients after radiotherapy should be treated with salvage surgery as far as possible.

Seven patients who relapsed in the lymph nodes belonged initially to T1 in one patient, T2b in four, and T3 in two. A local tumor ≥T2b would require some form of prophylactic lymph-node treatment. It must be further studied whether prophylactic radiation therapy to the cervical lymph-node stations is beneficial.

Because SCC of the eyelid is a disease of old patients, 12 out of the 14 patients who died succumbed to other concurrent diseases.

Regarding adverse events, severe late toxicities of Grade 3 or over were observed in nine patients(23.7%) and 12 events. Two patients (5.3%) lost their vision due to adverse events, which seems not to be inferior to other series considering that the patient population in this study included advanced T stage patients for whom protection of the lens and cornea was difficult. Proper selection of the electron-beam energy and lead-block insertion in 89% of the 38 patients probably contributed to lessen the incidence of loss of vision.

CONCLUSION

In conclusion, radical radiotherapy using electron beams for SCC of the eyelid yielded good results and could be a

treatment option. Advanced T stages (T3 and T4) and EQD₂ Gy < 56 Gy showed worse LRFR. After radical radiation therapy for eyelid SCC, close follow-up of local status is mandatory, because prompt surgical salvage of local relapse, although sometimes mutilating, is very effective. Whether dose escalation for advanced T stage and relapsed patients would improve LRFR, and whether prophylactic treatment to cervical lymph-node stations is warranted must be further explored.

CONFLICT OF INTEREST

Part of this study was financially supported by the Cancer Research Development Fund of the National Cancer Center (23-A-13).

FUNDING

This work was supported by the Cancer Research Development Fund (23-A-13) of the National Cancer Center, and the Cancer Clinical Research Fund of the Ministry of Welfare, Health and Labor.

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