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Japanese Journal of Clinical Oncology Advance Access published April 1, 2011

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011
doi:10.1093/jjco/hyr039

Original Article

A Long-term Follow-up Study of Prospective 80%-dose CHOP Followed by Involved-field Radiotherapy in Elderly Lymphoma Patients

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Received October 6, 2010; accepted March 2, 2011

Objective: The purpose of this study was to clarify the long-term clinical outcome of elderly patients with localized aggressive lymphoma and to explore appropriate treatment strategies for this population.

Methods: Subjects of this multicenter prospective study were untreated patients aged ≥70 years with aggressive Stage IA–IIA lymphoma. Therapy with 80%-dose CHOP (cyclophosphamide 600 mg/m^2, doxorubicin 40 mg/m^2, vincristine 1.1 mg/m^2 and prednisolone 80 mg/day for 5 days) was repeated every 3 weeks. After three cycles of chemotherapy, involved-field radiotherapy was performed with 30–50 Gy in 15–28 fractions.

Results: A total of 24 patients (median age, 75 years; range, 70–84 years) were enrolled. Nineteen patients (79%) had non-bulky tumors <6 cm. The median follow-up period was 7.3 years. The 7-year overall and progression-free survival rates were 78.9% (95% confidence interval, 62.3–95.5) and 65.3% (95% confidence interval, 45.3–85.3), respectively. Six patients developed systemic relapse, two of them after 6 years. The median survival time after relapse was only 5 months (range, 2 weeks–5.2 years). Five patients developed second malignancies, and three other patients died from other causes without lymphoma progression. None of the patients developed local relapse within the radiation field and/or regional relapse in adjacent lymph node areas.

Conclusions: Although systemic relapses, short survival time after relapse and death from other causes occurred, no loco-regional relapses were observed. Less intensive radiotherapy such as low-dose and small field might not compromise the treatment outcome for this population.

Key words: aggressive lymphoma – chemotherapy – geriatric oncology – dose intensity – radiotherapy

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a disease with high incidence in the elderly. The incidence rate of aggressive NHL increases with age (1). Nearly one-half of all newly diagnosed cases occur in patients older than 60 years (2), and the outcome of elderly patients is poor due to aggressive disease subtype and diminished organ function (2,3). Many clinical trials have demonstrated the benefits of systemic chemotherapy in patients with aggressive NHL, and standard treatment schedules, which can be applied to the majority of elderly patients, have been investigated (2,4). Some investigators have reported unacceptable toxicity due to aggressive therapy in elderly patients, and Balducci and Lyman (5) emphasized that patients older than 70 years are at high risk for neutropenic infection (6). In general, elderly patients have been considered too frail to receive the standard treatment and have instead received low-intensity treatment schedules. The US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program demonstrated that even in 1999, nearly 50% of elderly patients were still not receiving doxorubicin-based chemotherapy, which has gained general acceptance for use among the elderly (7). Older age, congestive heart failure and other co-morbidities are associated with treatment without doxorubicin.

On the other hand, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) conducted a prospective randomized trial to evaluate the administration of full-dose CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), with or without rituximab (Rituxan; Roche), in elderly patients (60–80 years old), and showed that these two full-dose regimens were safe for elderly patients aged $\leq$80 years (8). In general, patients participating in prospective clinical trials do not have severe co-morbidities and have good performance status, and thus full-dose chemotherapy is safe for such elderly patients. The gap between prospective clinical trials and clinical practice should be reduced to improve the level of clinical practice for elderly patients with NHL. To this end, we previously conducted a multicenter prospective study to evaluate the efficacy and safety of 80%-dose three-course CHOP followed by involved-field radiotherapy for elderly patients with localized aggressive NHL and reported that this regimen was safe for patients aged over 70 years (9).

The purpose of the present study was to clarify the clinical status of elderly patients after long-term follow-up and explore appropriate treatment strategies for elderly patients with localized aggressive NHL.

PATIENTS AND METHODS

Patients

Elderly patients aged $\geq$70 years with localized aggressive NHL were recruited between December 2000 and February 2004. Eligibility criteria were reported in detail previously (9). Histological subtypes were diffuse large B-cell, peripheral T-cell or anaplastic large cell lymphoma according to the World Health Organization classification, and localized diseases included Stage IA or IIA (10). All patients had good performance status (0–2) according to the Eastern Cooperative Oncology Group (ECOG) classification. Patients were excluded from the trial if they had a history of active cancer during the previous 5 years, co-morbidity with other serious medical conditions including severe ischemic heart disease or cardiomyopathy, positive serology for human immunodeficiency virus, or the presence of hepatitis B virus antigen or anti-hepatitis C virus antibody. All patients were required to have sufficient hematological, renal and hepatic function. Minimal staging procedures included clinical examination; chest radiography; gallium scintigraphy; computed tomography (CT) of the neck, chest, abdomen and pelvis; bone marrow biopsy; and blood studies. The staging procedure did not require positron emission tomography (PET).

This study complied fully with all provisions of the Declaration of Helsinki. All participating hospitals obtained the permission of their institutional review boards and all patients gave their written informed consent prior to entry into the study.

Treatment

The detailed treatment schedule and stopping rules were reported previously (9). Reduced-dose chemotherapy (80%-dose CHOP) included cyclophosphamide 600 mg/m^2 (day 1), doxorubicin 40 mg/m^2 (day 1), vincristine 1.1 mg/m^2 (day 1) and oral prednisolone 80 mg/day (days 1–5). Chemotherapy was repeated at 21-day intervals. If a patient developed Grade 4 neutropenia or febrile neutropenia, all subsequent cycles were administered with granulocyte colony-stimulating factor support.

Involved-field radiotherapy was performed after three cycles of chemotherapy. The involved field was defined as the regional area including the primary lesion and involved nodes determined by pre-chemotherapy evaluations, as well as adjacent uninvolved nodes. Examples include the full Waldeyer's ring and prophylactic bilateral whole-neck fields for Stage I tonsil lymphoma, and the ipsilateral neck field between the mastoid process below the tumor and the infraclavicular lymph node for Stage I lymphoma. The radiation dose was 30–30.6 Gy given in fractions of 15–20 Gy over 3–4 weeks in patients who achieved a complete response (CR) and 40–50 Gy in 20–28 fractions over 4–6 weeks for those who did not achieve CR. Response was assessed using Cheson's criteria, which did not include PET examination (11). Clinical examination was performed every 6 months for the first 5 years, and then at the discretion of the attending physician. Neck, chest and abdominal CT scans were performed after 6 months, and every 6 months thereafter during the first 5 years. After 5 years, clinical examination

was performed annually and continued for as long as possible.

Outcome Measures

Endpoints included overall survival (OS), progression-free survival (PFS) and relapse pattern. Survival was measured from the date of study registration. The last follow-up date of OS was the date of death, and that of PFS was the date of death or the date of disease progression (whichever came first). Data from patients who were alive at the last follow-up were censored. OS rate was calculated using death from any cause as an event, and PFS rate was calculated using disease progression or death from any cause as an event. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria grading system, version 2.0. OS and PFS rates were calculated using the Kaplan–Meier method. All patients were included in analyses of efficacy and safety. The log-rank test was used to compare survival distributions of different groups using a significance level of 0.05. Statistical analyses were performed with JMP software version 5.1 (SAS Institute, Cary, NC, USA). Tumor responses were classified as CR, CR unconfirmed (CRu), partial response (PR), stable disease or progressive disease according to the proposed International Workshop criteria (11).

RESULTS

Treatment Compliance and Toxicity

A total of 24 patients from eight Japanese institutions were enrolled in the study between December 2000 and February 2004. Patient characteristics are shown in Table 1. The most popular primary sites were Waldeyer's ring and other head and neck extranodal regions. The median age was 75 years (range, 70–84); four patients (16%) were >80 years. Three patients did not complete the study protocol; these patients received only two cycles of chemotherapy. The physician stopped the protocol in one patient, and another patient refused administration of the third round of chemotherapy. Another patient developed pancreatic cancer during chemotherapy, and the protocol was stopped. The compliance rate of the protocol was 87.5%. The administration of chemotherapy was delayed due to hematological toxicity in six patients, and the dose of chemotherapy was reduced due to hematological toxicity in one 84-year-old patient.

Severe non-hematological toxicity (Grades 3–4) during chemotherapy occurred in four patients (infection in three patients and diabetes mellitus in one patient). Non-hematological severe toxicity (Grade 3) during radiotherapy occurred in one patient (mucositis). None of the patients died from treatment-related toxicity.

Of the 22 patients who received radiotherapy at the head and neck area, we observed mild dry mouth in 10 patients at the last follow-up. None of the patients ate soft food due to the dry mouth and thus were administered a feeding tube.

Table 1. Patient characteristics

	No. of patients (%)
Age (years)	
Median	75
Range	70–84
70–75	15 (62)
76+	9 (38)
Gender	
Male	13 (54)
Female	11 (46)
Performance status (ECOG[a])	
0	18 (75)
1	6 (25)
Location	
Waldeyer's ring	11 (46)
Neck node	6 (25)
Maxillary sinus	3 (13)
Thyroid	2 (8)
Other sites	2 (8)
Stage	
I	16 (67)
II	8 (33)
LDH	
≤ULN[b]	20 (83)
>ULN, <1.5× ULN	4 (17)
≥1.5× ULN	0 (0)
Stage-modified International Prognostic Index[c]	
1	14 (59)
2	8
3	2 (8)
Tumor size	
<6 cm	19 (79)
>6 cm, <10 cm	4 (17)
≥10 cm	1 (4)

ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of the institutional normal range.
[a]Stage-modified International Prognostic Index; age (≥60 vs. >60), stage (I vs. II), serum LDH (normal vs. increased), performance status (0–1 vs. 2) [from ref. (17)].

Treatment Response and Survival Rates

Nineteen patients (79%) had a non-bulky tumor <6 cm in size. The response rate after chemotherapy and that after combined treatment were 79% (19 patients) and 88% (21 patients) for CR or CRu, respectively.

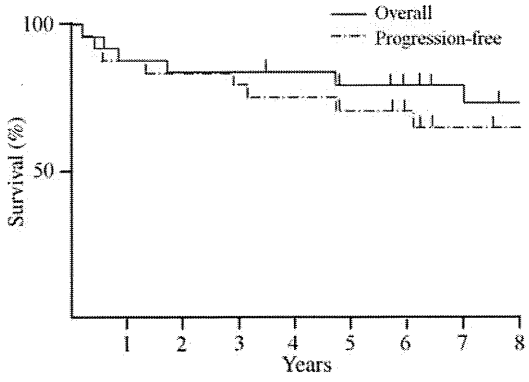

Figure 1. Overall and progression-free survival curves of the 24 patients.

The median follow-up period was 7.3 years (range, 0.3–9.3). The 7-year OS and PFS rates were 78.9% [95% confidence interval (CI), 62.3–95.5] and 65.3% (95% CI, 45.3–85.3), respectively (Fig. 1). All four patients aged >80 years survived longer than 4 years (4.8–8.9). The 7-year OS and PFS rates did not differ significantly with age (70–74 and 75+) ($P = 0.36$ and 0.79), stage (I and II) ($P = 0.77$ and 0.41) or stage-modified International Prognostic Index (1–3) ($P = 0.55$ and 0.59).

Relapse and Late Adverse Events

Six patients developed systemic relapse at distant sites: lung, heart, mediastinal lymph nodes, liver, adrenal gland, kidney, abdominal lymph nodes or bone marrow. Among these six patients, four had undergone the planned treatment schedule and had achieved CR or CRu after initial treatment, and two had undergone incomplete treatment and had achieved PR or stable disease. The median relapse interval from the start of initial treatment was 3 years (range, 5 months–8 years), and two patients developed systemic relapses after 6–8 years. After systemic relapses, these patients were treated with systemic chemotherapy and/or supportive care. The median survival time after relapse was only 5 months (range, 2 weeks–5.2 years). None of the patients developed local relapse within the radiation field and/or regional relapse in the adjacent lymph node areas during the follow-up period.

Five patients developed second malignancies: colon cancer in two patients, and gastric cancer, bladder cancer and pancreatic cancer in one patient each. The former four patients underwent curative surgery or endoscopic intervention. In the fifth patient, pancreatic cancer developed during initial lymphoma treatment, and he died 3 months after the present study registration. Three patients died due to other causes—cardiac failure, deterioration of general condition and sepsis without lymphoma progression—at 7 months, 4.8 and 9.3 years after registration.

DISCUSSION

More than half of all new cancer cases occur in patients aged ≥60 years. Despite the high frequency of cancer in this population, elderly patients have been underrepresented in clinical trials evaluating the standard of care for cancer, and few guidelines specifically address the evaluation and treatment of this population. Clinical trials have tended to exclude patients with co-morbid medical conditions, and physicians and patients prefer less toxic treatments in clinical practice. Among patients in the older age group, there is a large degree of heterogeneity in the ability to tolerate aggressive therapy, such as full-dose chemotherapy and/or definitive radiotherapy. Despite evidence that chronological age does not meaningfully influence the efficacy or toxicity of cancer treatment, elderly patients tend to receive less comprehensive cancer therapy compared with younger patients (12). This may be due to concerns of increased toxicity, coexistence of co-morbid medical conditions, and physician or patient preference. Predicting severe toxicity due to aggressive therapy plays a large part in treatment strategy decisions for elderly individuals. The treatment strategy for elderly patients should take into account the balance between harm and benefit. The Vulnerable Elders-13 Survey (VES-13) and comprehensive geriatric assessment (CGA) are useful tools for a geriatrician's baseline evaluation of an elderly individual (13). These programs are helpful for predicting toxicity due to treatment, estimating survival, identifying new problems during follow-up and improving general well-being (14–16). A weak point of our study was that we did not evaluate our study participants with VES-13 or CGA. In the future, these programs and other useful tools should be included in clinical trials to set the standard care for elderly patients with NHL.

The Southwest Oncology Group (SWOG) reported the effectiveness of three-course CHOP followed by involved-field radiotherapy in comparison with eight-course CHOP in patients with localized NHL (17). Three-cycle CHOP followed by involved-field radiotherapy was considered the standard care for patients with localized aggressive disease (18,19). Full-course chemotherapy is another standard type of care for patients with NHL. It was reported that elderly patients with NHL who had good performance status and minimal co-morbid illness could tolerate full-course chemotherapy without increased toxicity (20–22). However, in clinical practice, elderly patients have been considered too frail to receive the standard treatment and have been treated with low-intensity schedules (7). We performed a prospective study to evaluate the tolerability and effectiveness of short-course 80%-dose CHOP followed by radiotherapy and reported satisfactory tolerability and survival rates in the elderly (9). The addition of rituximab, a chimeric human/murine immunoglobulin G1 monoclonal antibody that binds specifically to the B-cell surface antigen CD20, to the full-course CHOP regimen was shown to improve treatment outcome in elderly patients with advanced disease with no accompanying increase in toxicity (8,23). The MabThera International Trial (MInT) Group demonstrated that the addition of rituximab improved treatment outcome in patients aged <60 years with low risk (24). However, the

clinical benefit of rituximab addition has not been clarified in patients with localized disease (25). SWOG conducted a Phase II study (SWOG0014) that evaluated four doses of rituximab plus three-course CHOP followed by radiotherapy in patients with localized aggressive NHL and reported 4-year PFS and OS of 88 and 92%, respectively (25). The SWOG8736 study applied short-course CHOP without rituximab in the same population and reported 4-year PFS and OS of 78 and 88%, respectively (17). These two different Phase II studies could not be compared using statistical analysis, and thus further studies are required. Given that the median survival time following relapse in the current study was only 5 months, initial effective treatment should be applied. Rituximab and other target therapies should be evaluated to develop a more effective and less toxic therapeutic strategy for elderly patients with aggressive localized NHL.

The SWOG studies applied relatively high radiation doses of 40 Gy or more. However, no prospective randomized trials have evaluated adequate radiation doses following chemotherapy in patients with NHL (26,27). Wilder et al. (26) conducted a retrospective analysis and reported that the local control rate in patients with tumors larger than 3.5 cm who received a radiation dose of $\leq$39.1 Gy was only 40%. However, this analysis included only a very small number of patients, which is problematic with regard to statistical analysis. Kamath et al. (27) reported that a radiation dose of $<$40 Gy led to a poor local control rate in patients with large tumors. However, in this study, the local control rate of good responders who achieved CR after chemotherapy was excellent even if they received low-dose radiotherapy (i.e. $<$30–40 Gy). Isobe et al. (28) reported a sufficient control rate in patients who received an intermediate radiation dose of 30–40 Gy following brief chemotherapy. Yu et al. (29) analyzed 86 patients with head and neck localized aggressive NHL who received short-course chemotherapy followed by irradiation of the involved node areas and reported that whole-neck irradiation including prophylactic irradiation of the contralateral neck area was not necessary. Our study included 19 patients (79%) with non-bulky tumor $<$6 cm and 16 patients (67%) with clinical Stage I lymphoma, and the response rate after chemotherapy was 79% (19 patients) for CR or CRu. Our study showed that none of the patients developed local relapse within the radiation field and/or regional relapse in the adjacent lymph node areas. Less intensive radiotherapy, such as low-dose radiation and the use of a small radiation field, should be investigated for the elderly population.

Our study indicated that late systemic relapses, short survival time after relapse, second malignancies and death from other causes occurred, and these adverse events were associated with failure to thrive, physical frailty and cognitive impairment. However, no loco-regional relapse was observed. Less intensive radiotherapy might not compromise treatment outcome for elderly patients with non-bulky and chemotherapy-responsive lymphoma.

Acknowledgements

The authors are grateful to Dr K. Yamamoto (Department of Hematology, Aichi Cancer Center Hospital), Dr T. Watanabe (Department of Hematology, National Cancer Center), N. Tsukamoto (Department of Hematology, Gunma University Hospital), Dr Y. Suzuki (Department of Radiation Oncology, Gunma University Hospital), Dr S. Takahashi (Department of Hematology, Cancer Institute Hospital) and Dr K. Murayama (Department of Hematology, Gunma Prefectural Cancer Center) for clinical support. The authors are grateful to Mrs Y. Asazawa and Mrs M. Kikuhara for technical assistance.

Funding

This study was supported by Health and Labor Sciences Research Grants (H21-018, H22-001), Grants-in-Aid for Cancer Research (20S-5) and a Grant-in-Aid for Scientific Research 'Third term comprehensive control research for cancer (H22-043)' from the Ministry of Health, Labor and Welfare of Japan. This study was presented in part at the 50th Annual Meeting of the American Society for Radiation Oncology, Boston, MA, USA, in September 2008.

Conflict of interest statement

None declared.

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Breast Cancer (2011) 18:252–258
DOI 10.1007/s12282-010-0206-9

Management of locoregional recurrence of breast cancer

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Received: 23 December 2009 / Accepted: 23 March 2010 / Published online: 7 May 2010

Abstract The locoregional recurrence of breast cancer is not a sign of distant metastases, and a substantial proportion of cases are cured by salvage therapy. Patients with locoregional recurrence should not be treated with palliative intent as if they have visceral metastases. The recommended treatment for ipsilateral breast recurrence after breast conservative therapy is a mastectomy. For patients who suffer from isolated chest wall recurrence after mastectomy, a surgical approach is recommended. Neoadjuvant chemotherapy is considered for patients with unresectable disease in order to render the disease resectable. For patients with isolated chest wall recurrence who have received no prior radiotherapy, postoperative radiotherapy involving the chest wall and regional lymph nodes is recommended. Patients with isolated axillary lymph node recurrence should be treated with axillary dissection or resection. Although the effectiveness of systemic therapy for patients with locoregional recurrence is unclear, there is a trend toward treating patients with supraclavicular lymph node recurrence with radiotherapy plus systemic therapy. Pain relief and the eradication of other distressing symptoms resulting from inoperable disease are achieved in two-thirds to three-quarters of patients by radiotherapy with or without systemic therapy. New anticancer agents and molecular target therapies should be evaluated with the objective of improving the treatment outcome of patients with locoregional recurrence. A combination of approaches is required for treatment of patients with locoregional recurrence, and a multidisciplinary tumor board should be organized at each institute.

Keywords Local recurrence · Lymph node recurrence · Radiotherapy · Chemotherapy · Mastectomy

Introduction

Ten to thirteen percent of patients who receive breast conservative therapy develop locoregional recurrence within 10 years of their initial treatment, and three to eight percent of patients who receive mastectomy plus postoperative radiotherapy will also develop locoregional recurrence [1]. The omission of postoperative radiotherapy increases the risk of ipsilateral breast recurrence or chest wall recurrence threefold. Ipsilateral breast recurrence after breast conservative therapy sometimes occurs after more than 10 years; however, approximately 80% of locoregional recurrences after mastectomy arise within the first 5 years [1–3]. The standard of care for locoregional recurrence has not been clarified because of its heterogeneous biological characteristics and a lack of well-designed prospective clinical trials. The authors have strived to assess the effectiveness of treatment strategies developed in previous studies.

Diagnosis and re-staging

The first step for choosing an appropriate treatment is pathological evaluation of the recurrent disease, and fine needle biopsy, core needle biopsy, and/or open biopsy can

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be used for this. The pathological subtype, histological grade, expression of hormonal receptors, and human epidermal growth factor receptor type2 (HER-2) overexpression should be evaluated when choosing appropriate treatment strategies for patients with recurrent disease. Radiation-induced sarcomas in the chest wall appear at a median of 10 years after postoperative treatment, but the latency period varies. The next step is a staging evaluation. Systemic disease can be carefully evaluated by using blood tests, chest computed tomography (CT), abdominal CT, pelvic CT, and radionuclide bone scans. Magnetic resonance imaging (MRI), CT, and color Doppler ultrasonography are useful for evaluating the extent of supraclavicular and infraclavicular lymph node recurrence. Positron emission tomography (PET) scans are performed increasingly in clinical practice and are more sensitive than CT and bone scans; however, meta-analysis of evaluation of breast cancer recurrence demonstrated that the false positive rate of PET scans was relatively high (11%) [4]. The clinical value of PET scans alone is not satisfactory, so addition of other conventional imaging modalities is required.

Prognostic factors

For patients with locoregional recurrence after breast conservative therapy, disease-free interval (DFI) from the initial treatment to recurrence is the most powerful predictive factor. The 5-year survival rate of patients who developed recurrence within 2 years of the initial treatment was 65% and that of the patients who developed recurrence after 2 years was over 80% [5]. Other poor prognostic factors of mortality have been reported, for example age (≥60 years), the number of positive lymph nodes at the initial treatment (four or more), primary tumor size (≥2 cm), histology (invasive cancer), and estrogen receptor expression (negative) [6]. For patients with locoregional recurrence after mastectomy, some tumor characteristics at the diagnosis of recurrence, for example an operable tumor, the absence of tumor necrosis, the recurrent site (chest wall or axillary lymph node), a pT1-2N0 primary tumor, and a long DFI, are associated with a good treatment outcome [7–9].

Schmoor et al. [9] reviewed 337 patients with locoregional recurrence among the 2,746 patients who received conservative therapy or mastectomy in four prospective studies of the German Breast Cancer Study Group. Multivariate analysis demonstrated that number of positive lymph nodes, tumor grade, estrogen receptor, and DFI were independent prognostic factors for progression-free survival after locoregional recurrence. They simplified the risk strata and defined three risk groups:

- low risk: primary node-negative status and a DFI of more than 2 years;
- intermediate risk: primary node-positive status or a DFI of more than 2 years; and
- high risk: primary node-positive status and a DFI of less than 2 years (Table 1).

Although it excludes other prognostic factors, for example age, tumor grade, recurrent site, and estrogen receptor, this simplified prognostic index is a useful tool for choosing treatment strategies in clinical practice and clinical trials.

Recurrence after breast conservative therapy

Thirteen percent of patients who develop recurrence after conservative therapy have locoregional recurrence alone, 30% have locoregional recurrence with distant metastases, and another 57% have distant metastases alone [2]. Approximately 80% of patients with locoregional recurrence develop ipsilateral breast recurrence as the first site [10, 11]. Recurrence in the ipsilateral breast includes two different types of disease, true recurrence and second primary tumors. True recurrence occurs within the primary tumor site or its vicinity, and second primary tumors occur in other quadrants of the breast or have a different pathological subtype [10, 12, 13]. However, some second primary tumors may occur in the same quadrant, and others will have the same pathological subtype. Strict distinction between true recurrence and second primary tumors is difficult, and some investigators have distinguished between them by using pathological subtype, location, and deoxyribonucleic acid (DNA) flow cytometry [10, 12, 13]. True recurrence is associated with early development (median interval: 3.7 vs. 7.3 years) and poor treatment outcome (10-year overall survival: 55 vs. 75%) compared with second primary tumors [12].

Table 1 Prognostic index for patients with locoregional recurrence of breast cancer [9]

	5-year PFS (95%CI)	5-year OS (95%CI)
Low risk		
Node (−) and DFI ≦2 years	53% (41–64)	66% (55–77)
Intermediate risk		
Node (+) or DFI >2 years	40% (31–49)	53% (44–62)
High risk		
Node (+) and DFI >2 years	17% (9–25)	27% (17–36)

Node (−), primary node-negative status; DFI, disease-free interval from initial treatment to recurrence; Node (+), primary node-positive status; PFS, progression-free survival; OS, overall survival; 95%CI, 95% confidence interval

Ipsilateral breast recurrence after breast conservative therapy

More than 20% of evaluated mastectomy specimens of ipsilateral breast recurrence after conservative therapy revealed substantial residual disease in two or more quadrants of the breast [14]. The generally recommended treatment for ipsilateral breast recurrence after breast conservative therapy is salvage mastectomy with or without axillary dissection [5, 6, 14–17]. Approximately 90% of the patients have operable recurrent tumors, and other patients have inoperative tumors with diffuse infiltration or inflammatory changes [11, 14–16, 18]. Most patients who received salvage mastectomy achieved good local control, and the 5-year overall survival rates after recurrence ranged from 60 to 86% [5, 6, 12, 14, 18]. Patients who have inoperative tumors involving diffuse infiltration or inflammatory changes have a poor prognosis [19].

Less intensive salvage care for locoregional recurrence has also been investigated. Several investigators have reported the outcome of repeated conservative therapy including partial breast resection with or without radiotherapy after ipsilateral breast recurrence [16, 18, 20]. Salvadori et al. [18] reported the same overall survival in patients who underwent re-conservative therapy (85%) and patients who received salvage mastectomy (70%); however, second ipsilateral recurrence was more common in the patients who received re-conservative therapy (19 vs. 4%). Galper et al. [16] reviewed 341 patients with local recurrence after conservative therapy and reported that the time to distant failure, second malignancy, or death of the patients who received re-conservative therapy was worse than that of the patients who received salvage mastectomy (hazard ratio: 2.0, $p = 0.02$). Re-conservative therapy for ipsilateral breast recurrence is not recommended. Sentinel lymph node (SLN) biopsy is a less toxic tool, and the experience of the Memorial Sloan–Kettering Cancer Center demonstrated that SLN were identified in 55% of 117 patients who had undergone prior axillary dissection or biopsy. Although SLN biopsy is available for some patients who have undergone prior axillary dissection, further studies are required [21].

Postoperative radiotherapy after salvage mastectomy is used for patients with a positive surgical margin or macroscopic residual tumor who have no history of breast irradiation. Re-irradiation is associated with late adverse effects such as tissue necrosis, fibrosis, and rib fractures. There are no data supporting prophylactic regional lymph node irradiation after salvage mastectomy for patients with ipsilateral breast recurrence.

Only one randomized clinical trial has evaluated addition of tamoxifen (TAM) for patients who underwent complete resection and postoperative radiotherapy [22]. Although the addition of TAM prolonged relapse-free survival, 9-year overall survival did not improve. Le et al. [23] reported that systemic chemotherapy and hormonal therapy reduced the risk of death for premenopausal patients, but did not reduce it for postmenopausal patients. Cochran's systematic review concluded that there was little evidence to support the addition of systemic therapy for patients with locoregional recurrence of breast cancer [24]. However, the addition of hormonal therapies is considered to be reasonable in selected patients because of their limited toxicities [25].

Regional lymph nodes recurrence after breast conservative therapy

Regional lymph node recurrence after breast conservative therapy is relatively rare (0.5–6.3%) [6, 26, 27]. The most common sites of regional recurrence are the axillary area and supraclavicular fossa [28, 29]. The pooled analyses of the National Surgical Adjuvant Breast and Bowel Project studies demonstrated that the prognosis of patients with isolated axillary lymph node recurrence was more favorable than that of patients with supraclavicular lymph node recurrence, and the 5-year distant metastases-free survival of the former was 31.5% whereas that of the latter was only 12.1% [6].

The experience of the MD Anderson Cancer Center was that surgery for axillary recurrence achieved good local control; however, the absence of radiotherapy or systemic therapy from the multimodality treatment strategy did not correlate with disease control or the frequency of distant metastases [30]. Maximum axillary control is achieved with an axillary dissection whenever feasible. Limited data are available regarding postoperative regional lymph node irradiation [28]. Radiotherapy is indicated for patients who undergo incomplete resection of axillary disease and patients with supraclavicular lymph nodes metastases [29]. Although the role of systemic therapy has not been established, there is a trend towards administering systemic therapy to patients with supraclavicular lymph nodes recurrence [17].

Fowble et al. [27] reported that none of their six patients with isolated axillary recurrence subsequently developed breast recurrence. They also concluded that isolated axillary node recurrence without clinical or mammographic evidence of ipsilateral breast recurrence does not require a prophylactic mastectomy.

Recurrence after mastectomy

According to the pooled analysis of the Easton Cooperative Oncology Group, locoregional recurrence developed in 420

patients among 2,016 patients who received mastectomy and adjuvant systemic therapy without postoperative radiotherapy [31]. Among 254 patients without simultaneous distant metastasis, isolated chest wall recurrence was found in 131 patients (52%), and locoregional recurrence with or without chest wall recurrence was found in 123 patients (48%). One hundred and sixty-six patients had locoregional recurrence and distant metastases simultaneously.

Isolated chest wall recurrence after mastectomy

Maximum local control of isolated chest wall recurrence is achieved with a wide excision whenever feasible [32–37]. Schwaibold et al. [36] reviewed 128 patients with isolated locoregional recurrence and reported that the 5-year overall survival and relapse-free survival rates of patients with a long DFI, surgical resection, and locoregional control were 61 and 59%, respectively. However, this favorable subgroup accounted for fewer than 20% of patients with isolated locoregional recurrence. On the other hand, aggressive surgery including extensive excision and reconstruction using skin grafts leads to a reduced quality of life, and, therefore, optimum treatment is achieved by balancing the potential benefits of local treatment with its adverse effects [38, 39]. If there is no clinical finding of axillary lymph node involvement, a prophylactic axillary dissection is unnecessary for patients who have undergone prior complete axillary dissection. The identification of SLN after prior axillary dissection is unlikely to be as successful as prior SLN biopsy alone (38 vs. 74%, $p = 0.0002$), and so SLN biopsy is not recommended for patients who have undergone prior complete axillary dissection [21].

Dahlstrom et al. [32] reported that 45% of patients had a new local recurrence after wide excision plus a 3-cm margin for isolated chest wall recurrence. In the study by Mallinckrodt, the 5-year freedom from chest wall re-recurrence of patients who received entire chest wall and regional lymph node irradiation was 75%, and that of patients who received small-field irradiation alone was 36% ($p = 0.0001$) [7]. Toonkel et al. [40] demonstrated that postoperative radiotherapy including chest wall and regional lymph node irradiation enhanced 5-year overall survival rates compared with chest wall irradiation alone (54 vs. 27%). The three-field or four-field technique including tangential chest wall fields and an en face supraclavicular area field are usually applied, even if the recurrent disease involves an isolated chest wall recurrence [32, 34, 36, 40–42]. The optimum daily fraction size is 1.8–2.0 Gy, and should be delivered five times weekly. The total dose administered to the initial field ranges from 45 to 50 Gy, with a boost of 10 to 20 Gy administered to areas of residual gross disease and the tumor bed. The biopsy scar should be covered by the bolus in order to obtain the optimum dose distribution [25]. In the MD Anderson Cancer Center, all areas treated prophylactically receive 54 Gy in 27 fractions, and all areas to be boosted because of microscopic disease receive an additional 12 Gy in 6 fractions [43].

A higher dose of definitive radiation for macroscopically residual tumors is associated with less in-field failure [7, 25]. It is difficult to obtain long-term local control in patients with diffuse inflammatory disease or unresectable disease. Neoadjuvant chemotherapy is considered for patients with unresectable disease in order to render the disease resectable, and radiotherapy is delivered after surgery. There is little information about re-irradiation after postoperative chest wall irradiation. Limited field re-irradiation using tailored conformal therapy techniques and concurrent chemoradiotherapy and/or twice daily fractionation regimens have been tested for patients with inoperative recurrent disease who had previously received radiotherapy [44, 45]. Re-irradiation of limited volumes with limited radiation doses can result in meaningful palliation for some patients.

Regional lymph nodes recurrence after mastectomy

Willner et al. [34] analyzed 145 patients with first locoregional recurrences after mastectomy and reported that the 5-year survival rate was better for patients with recurrences confined to the axillary lymph nodes (50%) than for those with recurrence confined to the supraclavicular lymph nodes (28%) or combined chest wall and axillary recurrences (28%). The 5-year survival rate of patients with supraclavicular lymph nodes recurrence and chest wall and/or axillary lymph nodes recurrence was only 5%.

Axillary lymph node recurrence after mastectomy

Axillary lymph node recurrence is rare after complete axillary dissection. Regional lymph node control for patients who receive axillary dissection after axillary recurrence is better than that for patients who receive radiotherapy alone [42]. Whenever feasible, a complete axillary dissection (Level I and II) is indicated for patients who have undergone prior SLN biopsy alone, and gross tumor resection is considered for patients who have undergone prior complete axillary dissection. Although the role of postoperative radiotherapy after salvage surgery is unclear, postoperative radiotherapy is used for patients who have not undergone prior axillary irradiation in some institutes [33, 34, 42, 46]. Radiotherapy should be considered for patients with incompletely resected disease or inoperable disease. The risk of symptomatic arm edema

after axillary dissection or axillary irradiation alone ranged from 4 to 8%; that after complete axillary dissection followed by radiotherapy was 36%, however [47].

Supraclavicular lymph node recurrence after mastectomy

Chen et al. [48] reviewed 63 patients with isolated supraclavicular lymph node recurrence among 3,170 breast cancers and reported that their 5-year survival rate was 33.6% and that surgical removal of the supraclavicular lymph nodes was associated with good overall survival after recurrence ($p = 0.03$). Although a surgical approach for supraclavicular lymph node recurrence is feasible, the clinical benefit of a surgical approach is believed to be small, because of the high frequency of local and distant relapse [49].

The clinical complete response rate for radiotherapy with or without chemotherapy ranged from 85 to 94%, the median time to progression was 28 months, and the 5-year overall survival rate after recurrence ranged from 21 to 35% [34, 46, 50]. Pergolizzi [51] compared 18 patients who received six-cycle chemotherapy alone with 19 patients who received initial three-cycle chemotherapy followed by involved-field radiotherapy and demonstrated that the local control of the former patients was worse than that of the latter patients (13 patients vs. 18 patients) and that the 5-year disease-free survival rate of the former was worse than that of the latter (5.5 vs. 21%, $p = 0.01$). Although there are no data supporting the use of systemic therapy for patients with locoregional recurrence, there is a trend toward the application of systemic therapy especially for patients with supraclavicular recurrence [23, 24, 34, 46].

Tumor infiltration of the brachial plexus induces shoulder pain, sensory changes in the fingers, and weakness and atrophy of the upper limbs. Radiation therapy is an effective local therapy for obtaining local control and avoiding distressing symptoms. Doses of 30–50 Gy are applied in 10–25 fractions over 2–5 weeks, and pain relief and the eradication of other distressing symptoms were achieved in more than two-thirds of patients [46, 50, 52]. Doses of 40 Gy or more were better at improving the distressing symptoms caused by supraclavicular lymph node metastases than those of less than 40 Gy (92 vs. 55%) [52].

New challenge

The 5-year overall survival rates of patients with ipsilateral breast or chest wall recurrence with simultaneous regional lymph node recurrence range from 7 to 24% [6, 34, 46]. Although systemic therapy has been commonly applied for patients with locoregional recurrence, the clinical benefit of systemic therapy including anthracycline-based and methotrexate-based regimens is uncertain. The clinical data regarding taxane-based regimens and molecular-targeted therapies, for example trastuzumab and lapatinib, should be evaluated using prospective trials, and a pilot study using hyperfractionated accelerated radiotherapy with or without systemic therapy has been conducted [44]. Additionally, patients with diffuse inflammatory disease and unresectable disease have an unfavorable prognosis. The optimum treatment for unresectable diffuse inflammatory recurrent disease needs to be established.

Locoregional recurrences of breast cancer have heterogeneous biological characteristics, and it is difficult to choose an appropriate treatment for each patient. Prospective clinical trials integrating adequate prognostic indices should therefore be conducted to define standard salvage treatment for patients with locoregional recurrence [9].

Conclusion

The optimum treatment for patients with locoregional recurrence requires a combination of modalities, and a comprehensive multidisciplinary treatment approach is essential. A multidisciplinary tumor board for breast cancer should be organized at each institute in order to propose an appropriate treatment for each patient.

Acknowledgments The authors are grateful to Mrs S. Yamauchi and Mrs N. Kamura for their technical assistance. This study was supported by Health and Labor Sciences Research Grants (H19-001, H19-003); Grants-in-Aid for Cancer Research (20S-5); and Grants-in-Aid for Scientific Research: "Third term comprehensive control research for cancer (H19-038)" from the Ministry of Health, Labor, and Welfare of Japan.

Conflict of interest statement The authors confirm that there are no actual or potential conflicts of interest in this article.

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平成19年5月18日第三種郵便物承認
第11巻・第1号 2011年12月25日発行
毎月1回25日発行 ISSN 2186-6589

特集

目でみる皮膚科学 ウィジュアル・ターマトロジー
Visual Dermatology

有棘細胞癌のすべて

責任編集 大原國章

2012
January
1
Vol.11 No.1

Part 1. SCCの前駆症状

熱傷瘢痕／慢性放射線皮膚炎／DLE／色素性乾皮症／慢性骨髄炎／
褥瘡／粉瘤／長期の外用PUVA療法／白板症／
疣贅状表皮発育異常症／慢性膿皮症／外傷瘢痕

Part 2. SCCの病理組織像 ①SCCのタイプ

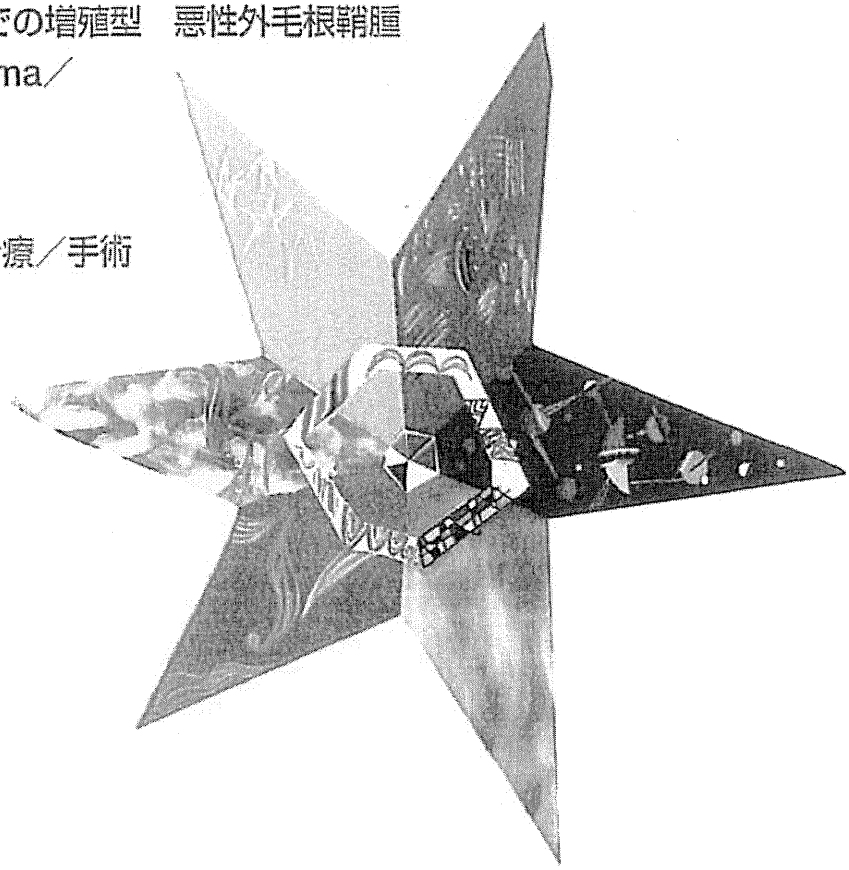
疣状癌(verrucous carcinoma)／色素性有棘細胞癌／
偽腺性有棘細胞癌(pseudoglandular SCC)／
spindle cell squamous cell carcinoma

Part 3. SCCの病理組織像 ②SCCとの異同

日光角化症／Bowen病／
毛包癌 その1 嚢腫性病変／
毛包癌 その2 被覆表皮での増殖型　悪性外毛根鞘腫
malignant tricilemmoma／
ケラトアカントーマ

Part 4. SCCの治療

動注化学療法／放射線治療／手術



秀潤社

Visual Dermatology

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J Visual Dermatol 11:74-77,2012

放射線治療

鹿間 直人

Key words: 有棘細胞癌，放射線治療，電子線照射

はじめに

有棘細胞癌では，手術療法を中心とした治療が主に行われている．しかし，高齢者，切除不能例，顔面などに発生し整容性や機能面で手術が望ましくない症例などに対しては，放射線治療が行われる[1]．

過去の放射線治療に関する報告を見ると，1回線量が現在用いられるものよりもかなり高く，また放射線治療の精度も低く，放射線治療後の晩期障害の頻度が高く整容性も不良であった．しかし最近では，放射線治療技術の進歩と放射線治療の品質管理，適正な照射スケジュールなどを用いることで，優れた局所制御と整容性を確保することが可能となった[1]．本稿では，有棘細胞癌における放射線治療と局所制御について述べる．

放射線治療機器の種類と照射スケジュール

一部の施設を除いて，電子線と超高圧X線（以下X線）が使用可能な機器が広く普及している．表在性腫瘍に対しては，電子線を用いて治療が行われる．腫瘍の深さと拡がりを理学的所見や画像などで評価し，電子線のエネ

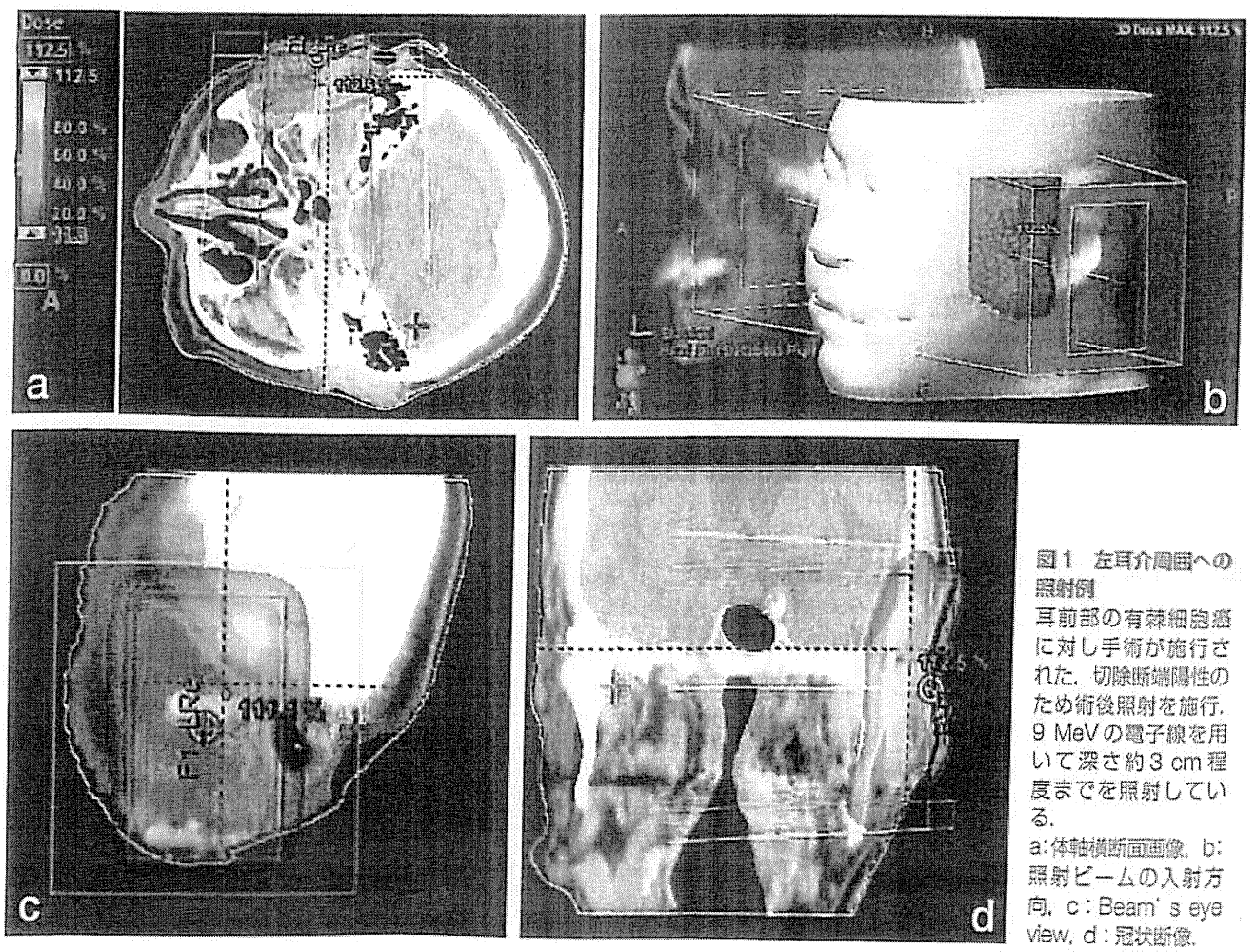

図1 左耳介周囲への照射例
耳前部の有棘細胞癌に対し手術が施行された．切除断端陽性のため術後照射を施行．9 MeVの電子線を用いて深さ約3 cm程度までを照射している．
a：体軸横断面画像，b：照射ビームの入射方向，c：Beam's eye view，d：冠状断像．

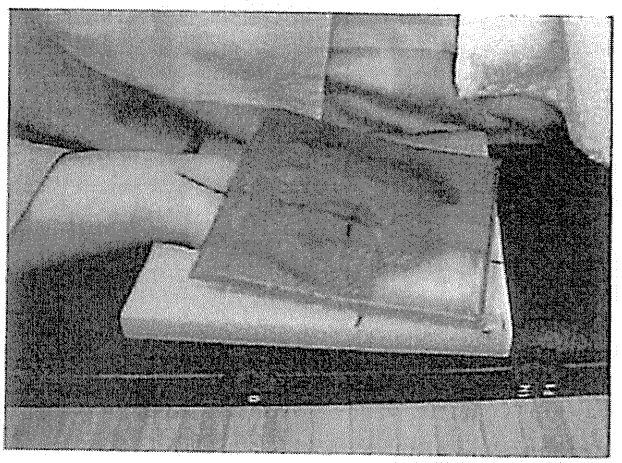

図2　ボーラス材
放射線の吸収率が水と同じ材質でできた軟らかい素材を皮膚表面に載せ，ビルドアップ現象による皮膚表面の線量低下を解消する．

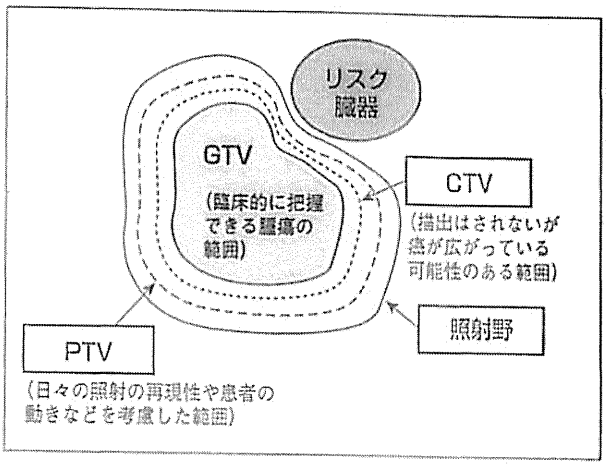

図3　照射野形状の概念図
リスク臓器が近接している場合には，各マージンを小さく設定することもある．

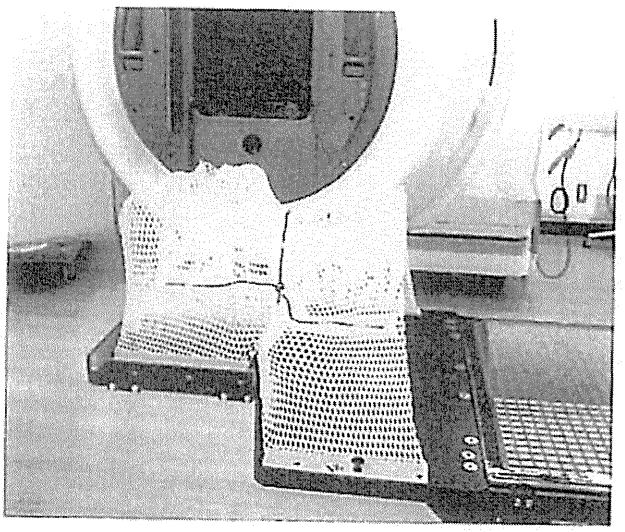

図4　固定具
患者個別に固定具を作成することで，日々の照射野の再現性を確保する．

ルギーを変えることで約5 cm程度までの深さの腫瘍を治療することが可能である（図1）．

これ以上に厚みのある病巣や深部に浸潤した病変に対しては，X線が用いられる．電子線およびX線とも皮膚表面の線量はビルドアップ現象のために低下してしまうため，皮膚線量を高める工夫として，放射線の吸収率が水と等価の材質でできたボーラス材を用いる（図2）．

現在，推奨される照射スケジュールとしては，小さな腫瘍に対しては55 Gy（グレイ）/20分割/4週間や50 Gy/15分割/3週間で治療する方法が推奨されている．また，腫瘍が大きく広範囲に照射する必要がある場合や重要臓器が近接する場合には，より1回線量を低減させ，総線量66～70 Gy/33～35分割/6.6～7週間で治療することが推奨されている[1]．

放射線治療の計画方法

放射線治療を開始する際には，皮膚科医と放射線医の密な連携が必要であり，腫瘍の進展範囲や深部方向の進展度などの情報を正確に把握しなければならない．必要な照射野の形と大きさを整形するために，患者個別の鉛ブロックを作成することもある．

一般的に有棘細胞癌で2 cm以下の小さな腫瘍では約1 cm程度の，これを超える腫瘍では1.5 cmのマージンをつけた臨床標的体積（CTV：臨床的に把握される腫瘍の範囲と腫瘍が進展している可能性があると判断される範囲を合わせた範囲）を設定する．計画標的体積（PTV：CTVに日々の照射野の再現性や患者の動きなどを考慮した範囲）のマージンとしては，約5 mm程度を設定する．眼球などの重要臓器（リスク臓器）が近接している場合には，重篤な遅発性有害事象を避けるため，CTVやPTVのマージンを小さく設定せざるを得ないこともある（図3）．

リスク臓器が近接しており照射野を可能な限り小さくしなければならない場合には，日々の照射野の再現性を高め，PTVマージンを小さくする工夫が必要である．顔面への照射では固定具（シェルなどとよばれている）を患者ごとに作成するべきである（図4）．手指の遠位側に発生し，ほかの手指に癌が進展する可能性が低いと判

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総説 2 放射線治療

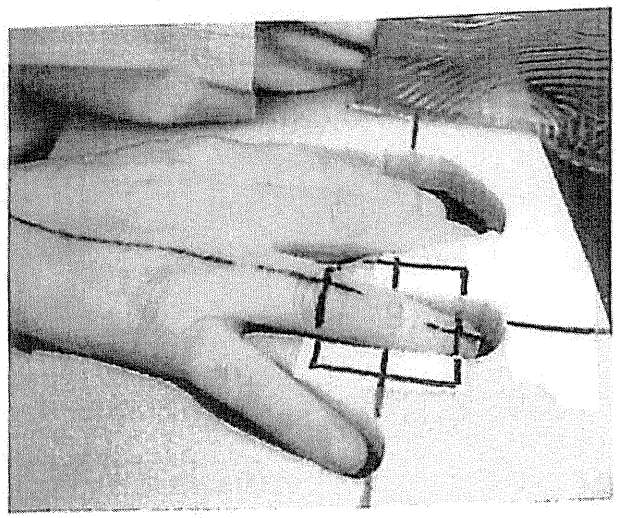

図5 指への照射
環指にできた有棘細胞癌に対する放射線治療．ほかの指を照射野外に外すため指を広げ，指を固定する治具を作成し照射を行った．

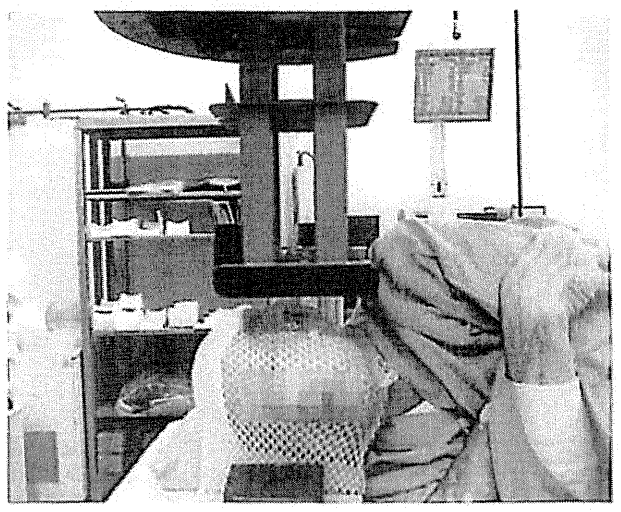

図6 耳介周囲への照射
外耳道が照射野内に含まれないよう，鉛の板で外耳道を遮蔽している．

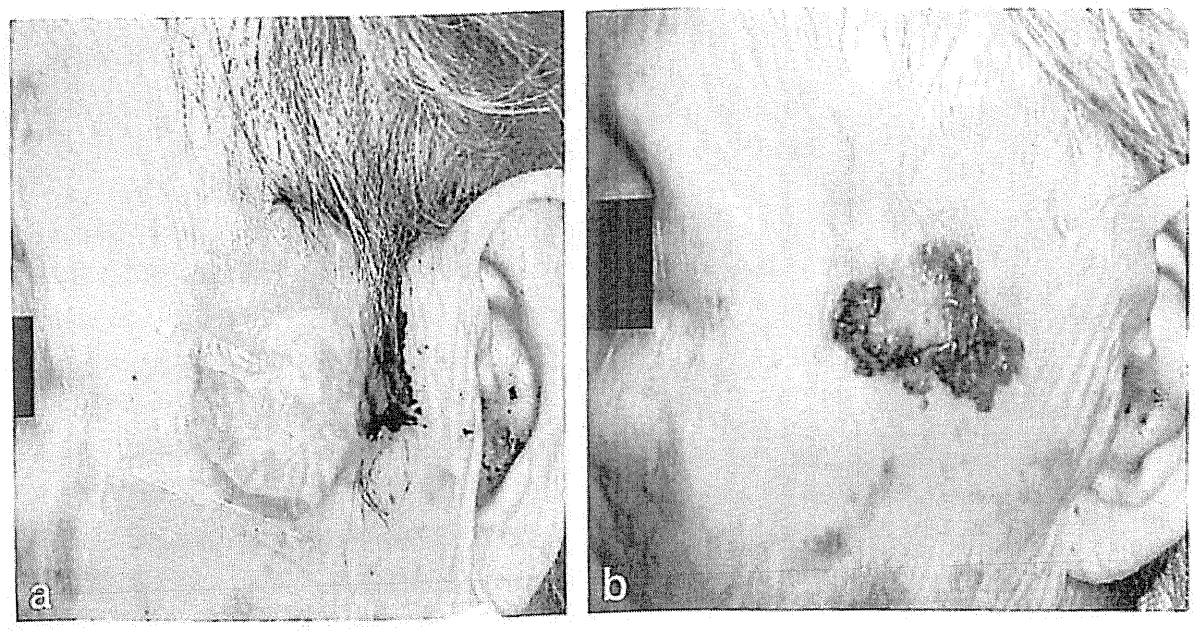

図7 100歳代，女性．左顔面の有棘細胞癌
(a) 放射線治療前．高齢であり，放射線治療が選択された．
(b) 放射線治療終了直後．電子線を用いて55 Gy/20分割/4週間の放射線治療を行った．

断される場合には，ほかの手指を確実に照射野外に外すための治具を作成し，より毒性の低い治療を心がける（図5）．耳介周囲の照射では遮蔽に鉛の板が用いられる（図6）．

おわりに：実際の治療例

放射線治療は皮膚癌において有用な治療の一つであり，手術困難な症例や手術では整容性や機能面が低下することが予想される症例を中心に用いられる（図7，8）．患者個別の対応が要求されることも多く，放射線技師や医学物理療法士の協力が必須である．

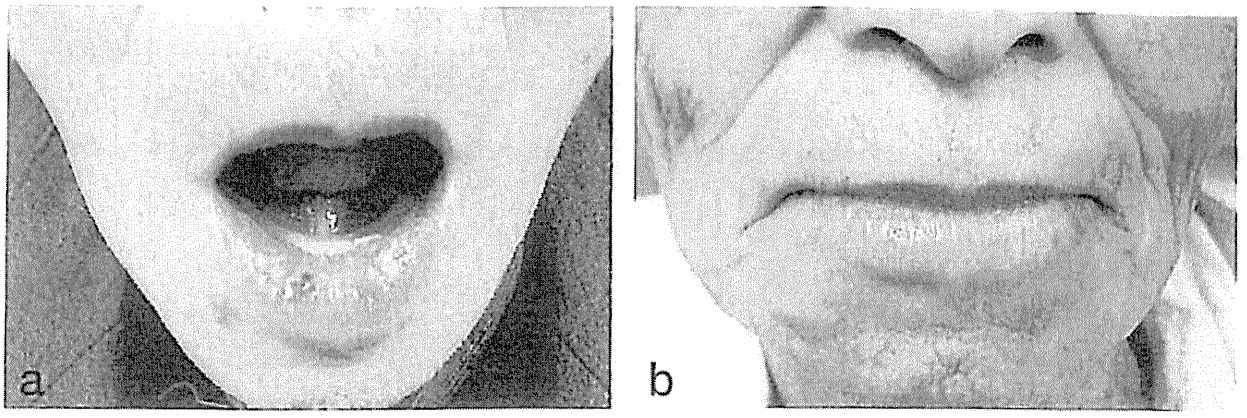

図8　70歳代，男性．下口唇に発生した扁平上皮癌
(a) 放射線治療前．機能面および整容性が考慮され，放射線治療が選択された．
(b) 放射線治療後3カ月．電子線を用いて66 Gy/33分割/6.6週間の放射線治療を施行した．

文献

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