Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 1, pp. 251–258, 2009
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0360-3016/09/$–see front matter

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doi:10.1016/j.ijrobp.2008.03.049

CLINICAL INVESTIGATION **Cervix**

PROSPECTIVE STUDY OF ALTERNATING CHEMORADIOTHERAPY CONSISTING OF EXTENDED-FIELD DYNAMIC CONFORMATIONAL RADIOTHERAPY AND SYSTEMIC CHEMOTHERAPY USING 5-FU AND NEDAPLATIN FOR PATIENTS IN HIGH-RISK GROUP WITH CERVICAL CARCINOMA

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Purpose: To assess the efficacy of alternating chemoradiotherapy combined with extended-field conformal radiotherapy for patients with high-risk cervical cancer.

Methods and Materials: Patients with previously untreated cervical cancer, with Stage III/IVA disease, or Stage IB/II with high-risk factor (primary tumor diameter ≥50 mm or positive lymph node) were entered into this study. Three cycles of chemotherapy with 3,500 mg/m^2 of 5-fluorouracil (5-FU) and nedaplatin (NDP) were accompanied with pelvic irradiation of 45.6–51.3 Gy in 24–27 fractions over 6 weeks. Prophylactic (36 Gy/20 fractions) or definitive (45–56 Gy) irradiation for para-aortic region was followed by pelvic irradiation.

Results: Between 1998 and 2004, 40 patients were recruited for this protocol study. Eighteen patients from Phase I setting were registered. Twenty-two patients were treated with NDP of 140 mg/m^2 (the recommended dose) in the Phase II segment. Twenty-five patients had T3 disease, and 25 patients had nodal disease including para-aortic involvement ($n = 5$). Overall/progression-free survival rates at 5 years were 78.8 and 66.5%, respectively. The median follow-up time was 61.8 months (25.5–106.7). Hematologic and gastrointestinal Grade 3 or more toxicities were relatively high rate (27.5–45%); however, they were well manageable. Two for bladder toxicity of Grade 3 were noted. Comparing the data from historical control group evaluated by magnetic resonance imaging, alternating chemoradiotherapy revealed a significant favorable factor for survival and disease recurrence in multivariate analysis ($p < 0.05$).

Conclusion: Acquired results from our unique protocol for cervical cancer with high-risk factor were thought to be promising, considering that the majority of our cohort consisted of high-risk population. © 2009 Elsevier Inc.

Extended field, Alternating chemoradiotherapy, Nedaplatin, Cervical cancer, Conformational radiotherapy.

INTRODUCTION

Standard treatment for patients with advanced-staged cervical carcinoma is now believed to be concurrent chemoradiotherapy. Chemoradiotherapy improves overall survival (OAS) and progression-free survival (PFS), whether or not platinum was used. Absolute benefit was reported as 10% advantage of OAS and 13% of PFS (1). Chemoradiation showed a significant benefit for local recurrence and a suggestion of a benefit for distant recurrence, although this trend was more markedly noted among patients with Stage I-II disease compared with those of Stage III -IVA (2–5). Contents of chemotherapy regimen was varied much, although weekly administration of cisplatin was now widely used because Gynecologic Oncology Group (GOG) 120 could not showed an apparent advantage of addition of 5-fluorouracil (5-FU) compared with single use of cisplatin (2, 6).

Nedaplatin (NDP) is an active agent for cervical carcinoma (7), shown to have treatment effects equivalent to those of the widely used cisplatin but with less renal and gastrointestinal toxicity (8). Its dose-limiting toxicities (DLT) are thrombocytopenia and myelosuppression, and its recommended dose (RD) in Japan is 100 mg/m^2. However, we have reported the possibility of dose escalation of NDP when used in combination with 5-FU before the administration of NDP. In our previous report, the RD of NDP was 150 mg/m^2 (9). Theoretically, the antitumor effect of concurrent administration is

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Conflict of interest: none.

Acknowledgment—Parts of this article were presented at the 46th and 49th Annual Meetings of American Society for Therapeutic Radiation Oncology (ASTRO), October 3–7, 2004, Atlanta, GA, and October 28–November 1, 2007, Los Angeles, CA.

Received Feb 14, 2008, and in revised form March 12, 2008. Accepted for publication March 27, 2008.

identical, but the increasing acute toxicity is an important problem. Thus the intensity of both radiotherapy and chemotherapy would be compromised in this setting. Alternating chemoradiotherapy (ALCRT) is a method for resolving this problem; avoiding the concurrent usage of these two modalities may reduce the acute toxicity, allowing the full dose of chemotherapy to be maintained. We have also reported excellent outcomes of ALCRT in nasopharyngeal cancer (10). As with nasopharyngeal cancer, patients with cervical cancer with advanced stage had hazard of metastatic disease progression, so intensity of chemotherapy is thought to be an important issue for patient management.

To investigate the efficacy and feasibility of ALCRT for high-risk cervical carcinoma, we performed a Phase I/II study at our institution.

METHODS AND MATERIALS

Eligibility criteria

Previously untreated patients with histologically diagnosed as squamous cell carcinoma of uterine cervix were entered into this study. Eligible patient was defined as having a high risk factor (Stage I-II; tumor size ≥50 mm or positive pelvic node OR all Stage III-IV disease); good performance status (PS), adequate organ function; age 20–75; and informed consent. Importance of prognostic indicator of magnetic resonance imaging (MRI) has been reported multi-institutional study (11, 12), and we take account for patient selection for this protocol. Patients with lymph node metastasis limited to para-aortic region who were diagnosed by imaging are also included this study.

Before enrollment, each patient underwent complete physical, laboratory, and stage assessments. The laboratory examinations consisted of complete blood count, serum chemistry, 24-h creatinine clearance, and electrocardiography. The staging workup included chest radiography, computed tomography (CT) of the whole abdomen, and pelvic MRI. Lymph nodes measuring 10 mm or more along the long axis on CT or MRI scan was defined as metastatic nodes. Patients were required to have a white blood cell count ≥3,000/μL, platelet count ≥100,000/μL, hemoglobin level ≥10.0 g/dL, normal hepatic (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level <2.5 times the upper normal limit) and renal function (24-h creatinine clearance level ≥60 mL/min), and normal electrocardiogram. Written informed consent was obtained from all patients. The protocol was approved by the institutional review board.

Response and toxicity evaluations

To evaluate responses and toxicity, all patients underwent complete blood count and serum chemistry analysis one to two times per week. The response evaluation was judged 2 months later from last day of whole treatment. Response evaluation was done with physical examination with smear cytology, pelvic MRI scan, and whole-abdominal CT scan.

Magnetic resonance imaging was repeated every 3–4 months for the first 2 years and twice per year thereafter. A CT scan of the whole abdomen was repeated every 6 months. Toxicity was assessed and graded using the National Cancer Institute Common Toxicity Criteria, version 3.0. The grading of late urinary and gastrointestinal toxicities due to radiotherapy was in accordance with the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer toxicity criteria (13). The DLT were defined as Grade 4 hematologic toxicities or any nonhematologic Grade 3 or higher toxicities, except diarrhea, nausea, and vomiting. The chemotherapy dose and schedule modifications for toxicity are shown in Table 1.

Phase I component

The primary end point of the Phase I part of the study was to determine the maximum tolerated dose (MTD) and the RD of NDP for the Phase II segment, when combined with 120-h infusion of 3,500 mg/m^2 5-FU and definitive radiotherapy on an alternating schedule, for patients with cervical cancer with high-risk factors.

Dose escalation scheme

The starting dose of NDP was 100 mg/m^2, as suggested by a previous study (9). Additional increases of 20 mg/m^2 up to the MTD were permitted. According to our previous report, the dose of NDP did not exceed 150 mg/m^2 (9). At least 3 patients were treated at each dose level. The end point to close the study was a DLT if observed in 2 of 3 patients or in 3 of 6 patients at the same dose levels.

Table 1. Chemotherapy and radiotherapy dose and schedule modifications for toxicity

Toxicity	Modifications
Chemotherapy	
Grade 4 leukopenia, granulocytopenia	25% reduction of both nedaplatin and 5-FU
Grade ≥3 thrombocytopenia	25% reduction of both nedaplatin
Grade 2 renal dysfunction	
Grade ≥3 diarrehea	25% reduction of 5-FU
Grade 2 liver dysfunction	
Grade ≥3 liver or renal reaction	Withheld additional chemotherapy
Nonhematologic Grade >3: toxicity, except for nausea/vomiting	Chemotherapy postponed until recovery
Radiotheraphy	
Grade 4 leukopenia, granulocytopenia	Postponed until recovery to Grade 2
Grade 4 thrombocytopenia	Postponed until recovery to Grade 2
Grade 3 leukopenia, granulocytopenia, and infection or Grade 2 fever	Postponed until recovery of infection and fever
Schedule modification	
Chemotherapy was started with a white blood cell count ≥2, 500 μ^{-1}, platelet count ≥100, 000 μ^{-1}, hemoglobin level ≥8.0 g dl^{-1}, total bilirubin ≤2.0 mg/dL serum creatinine ≤1.2 mg/dL, and esophagitis Grade ≤3. If these data did not fulfill the criteria, radiotherapy was continued until these data recovered . As soon as these data improved, the next cycle of chemotherapy should be started, resting radiotherapy between courses of chemotherapy.	

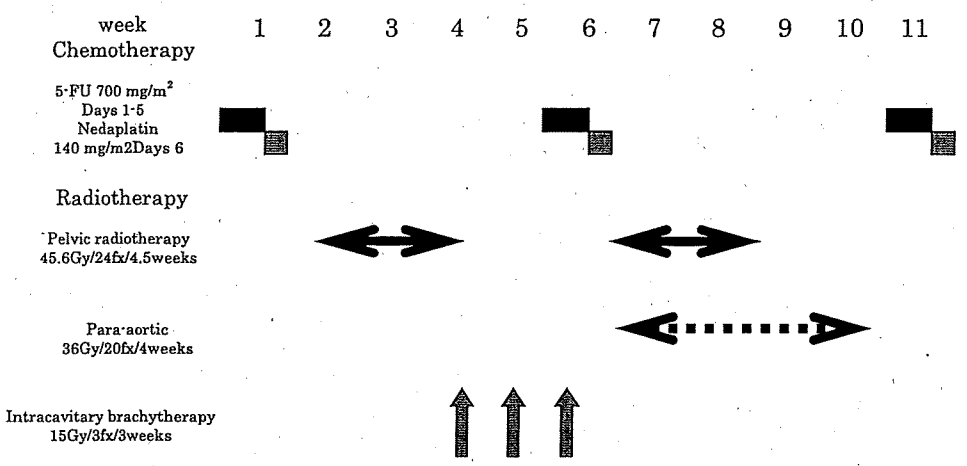

Fig. 1. Treatment scheme of the Phase I/II study of alternating chemoradiotherapy with nedaplatin and 5-FU in patients with advanced cervical carcinoma.

The previous doses before the MTD were considered the RD for the Phase II study.

Phase II component

The primary end point of the Phase II segment of the study was PFS of alternating chemoradiotherapy at the RD. The secondary end points were the OAS and the feasibility of this protocol. The same patient eligibility requirements, treatment schedules, dose and schedule modifications, and response and toxicity criteria as in the Phase I part of the study applied.

Treatment schedule and modifications

Chemotherapy. The treatment scheme is shown in Fig. 1. Prophylactic antiemetics therapy, using a 5-hydroxytryptamine type III receptor blocker and dexamethasone was given to all patients. The details of the administration of chemotherapy have been reported (9, 14). The dose of NDP was elevated to find MTD. MTD was decided to dose limiting toxicities as to Grade 4 of hematologic toxicities and Grade 3 of nonhematologic toxicities excluding diarrhea and nausea/vomiting. After deciding RD, patients were treated with RD of NDP.

Radiotherapy. Radiation therapy using a megavoltage photon beam (6–10 MV) by linear accelerator (CLINAC; Varian Medical Systems) was started 1–2 days after the end of systemic chemotherapy. The gross tumor volume (GTV) was defined as the total volume of the primary tumor evaluated by MRI scan (GTV primary) and the involved lymph nodes (GTV node) assessed by either MRI or abdominopelvic CT scan. A patient with lower vaginal involvement was arranged the adequate inferior margin of radiation field for tumor extent using iodine powder or metallic ring at planning set-up. The clinical target volume (CTV) for involved lymph node (CTV node) was defined as the GTV node with 1cm margin in every direction. CTV pelvis was defined as entire uterus and regional pelvic lymph node according to the guidelines of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer consensus. CTV pan was defined as para-aortic lymph node region located up to upper border of the 12th thoracic spine. In general, CTV pan was included both inferior vena cava and abdominal aorta with 1-cm margin for every direction. The planning treatment volume (PTV) for involved lymph node (PTV node) was defined as the CTV node with a 0.5–1 cm margin. The PTV pelvis and PTV pan was defined as the CTV plus a 0.5–1 cm margin in all directions. Radiotherapy was given with daily 1.9 Gy fractions to 45.6 Gy in 24 fractions for PTV pelvis by biaxial dynamic conformal radiation therapy (11, 12, 15). If patients had a positive pelvic lymph node, they received 51.3 Gy of 27 fractions to PTV pelvis followed by an additional boost dose for PTV node up to a total dose of 57.3 Gy. Patients with positive pelvic lymph node or diagnosed as Stage III or more stage received a prophylactic para-aortic lymph node irradiation of 36 Gy with 20 fractions was planned by dynamic conformal radiotherapy (15). Patients with positive lymph node on para-aortic region receive an additional boost to PTV node up to 54 Gy. Radiotherapy was interrupted during the administration of the second and third cycles of chemotherapy. Intracavitary brachytherapy (ICBT) was accompanied with external beam radiotherapy (EBRT). Both EBRT for PTV primary and ICBT should not be treated in same day. During treatment course, MRI of the pelvis was taken to evaluate response. If primary tumor was thought to shrink to a sufficiently small volume within the high-dose volume of ICBT, brachytherapy was started. All EBRT was planned by radiation treatment planning system FOCUS or XiO (CMS Inc.). Before March 2002, the source of intracavitary brachytherapy was radium, and then was replaced with iridium. High-dose-rate ICBT was delivered using microselectron. The radiation therapy dose and schedule modifications for toxicity are shown in Table 1.

Statistical considerations

The survival time was defined as the period from the start of treatment to death or the last follow-up evaluation, and the PFS was defined as the period from the start of treatment to progression of disease or death, for any reason. The statistical differences between the two groups were assessed with the chi-square test. The OAS and PFS curves were calculated using the Kaplan-Meier method (16). The log–rank test (17) was used to compare survival curves. Cox-proportional hazards model (18) was used for a multivariate analysis.

RESULTS

Characteristics of patients

Between September 1998 and December 2004, 40 patients at the Aichi Cancer Center Hospital, Japan, were enrolled in this Phase I/II study. The patient characteristics of each group are shown in Table 2.

In the Phase I segment, 18 women were enrolled. In the Phase II segment, 22 women were enrolled using RD of NDP.

Phase I study

Dose escalation and toxicity. The principal toxicities observed in the Phase I study are summarized in Table 3. At the first dose level (100 mg/m^2), none of the 3 patients had DLT. At the second dose level (120 mg/m^2), 1 case of Grade 4 thrombocytopenia developed among the 6 patients. This dose level was considered safe, and the dose was increased to the next level. At the third dose level (140 mg/m^2), one case each of Grade 3 liver dysfunction and diarrhea developed among 6 patients. In next dose level (150 mg/m^2), two cases of neutropenia in 3 patients developed, then the MTD was determined to be 150 mg/m^2 and an RD of 140 mg/m^2 was used in the Phase II part.

Completion of therapy. As shown in Table 2, 23 of 40 patients were able to receive three cycles of chemotherapy. Four patients reduced their doses of NDP during the second cycle of chemotherapy. Twenty-three (58%) patients received the third cycle of systemic chemotherapy, but the NDP dose had to be reduced in 4 of these patients. Two patients received only a single cycle of chemotherapy because of toxicities. The 5-FU dose was not reduced in any patients in the Phase II part of the study. Delay or inability to administer the third cycle of chemotherapy was chiefly from hematologic toxicities.

Table 2. Patient characteristics and treatment contents

Factors	Number
Age (y)	54 (34–74)
Performance status	
0	4
1	36
T stage	
1b	
2a	2
2b	10
3a	3
3b	22
N stage	
0	15
I	25
FIGO stage	
I	3
II	11
III	21
IV	5
Maximum tumor size (mm)	61 (35–100)
Radiation theraphy	
EBRT	
Pelvic region (Gy)	53.6 (41.8–64.6)
Paraaortic region	36 (14.4–54)
OTT(days)	51 (34–78)
ICBT	
Source	
Radium	24
Iridium	16
A point dose	23.1 (7.5–27.6)
Fraction	2 (1–4)
Chemotherapy	
Dose of NDP (mg/m^2)	
100–120	9
140	28
150	3
Cycle of chemotherapy	
1	2
2	15
3	23

Table 3. Results of Phase I component

NDP (mg/m^2)	100	120	140	150	Total
Leukopenia	0/3	0/6	0/6	2/3	2/18
Anemia	0/3	0/6	0/6	0/3	0/18
Thrombocytopenia	0/3	1/6	0/6	0/3	1/18
Liver	0/3	0/6	1/6	0/3	1/18
Renal	0/3	0/6	0/6	0/3	0/18
Diarrhea	0/3	0/6	1/6	0/3	1/18
Emesis	0/3	0/6	0/6	0/3	0/18
Vomiting	0/3	0/6	0/6	0/3	0/18
Fever	0/3	0/6	0/6	0/3	0/18
Stomatitis	0/3	0/6	0/6	0/3	0/18
Total	0/3	1/6	2/6	2/3	5/18

A median dose of 53.6 Gy (range, 41.8–64.6 Gy) was administered to pelvic lesion by EBRT. All patients received ICBT using low-dose-rate or high-dose-rate ICBT. The median dose of sum of point A dose of ICBT was 23.1 Gy ranged from 7.5 to 27.6 Gy. All patients could be treated with planned pelvic radiotherapy including ICBT. The median dose of para-aortic region was 36 Gy (range, 14.4–54 Gy). Para-aortic irradiation stopped in 2 patients at 14.4 Gy and 18 Gy because of acute gastrointestinal toxicity. Five patients received an additional radiotherapy to involved para-aortic lymph node with a dose of 46–54 Gy using cone down technique.

Treatment outcomes

Response and survival. The following 22 patients were treated with dose level of RD. Between 1998 and 2004, 65 patients were treated with this protocol, and 40 patients of 65 were evaluated for treatment efficiency. The reasons for exclusion of 25 patients were patient's age, previous treatment before chemoradiotherapy, and refusal of chemotherapy. Thus we evaluated these 40 patients including Phase I study regarding to treatment outcome and feasibility. At the median follow-up of 61.8 months (range, 8.6–106.7 months), 10 patients had died of the disease, 3 were alive with the disease, and 27 were alive without disease.

The OAS and PFS rates at 5 years were 78.8% (95%CI, 65.6–92.1%) and 66.5% (95%CI, 51.4–81.6%), respectively.

Four patients had residual tumor or disease progression at the primary site, and 5 patients had relapses at the pelvic region with or without local failures. Eight patients had distant metastasis during the follow-up period. The OAS and PFS rates were not significantly different between patients received three cycles of chemotherapy and those with one or two cycles ($p > 0.05$).

Table 4. Adverse event of acute adverse event in alternating chemoradiotheraphy with all 40 patients

	1	2	3	4	% of toxicities Grade 3
Leukopenia	4	10	25	1	65
Neutropenia	4	14	14	5	47.5
Anemia	4	21	7	7	35
Thrombocytopenia	12	8	10	8	45
Liver	13	10	3	0	7.5
Renal	10	1	0	0	0
Diarrhea	14	15	9	2	27.5
Emesis	4	19	17	0	42.5
Vomiting	15	25	0	0	0
Fever	0	13	1	0	2.5

Toxicity

The toxicities observed in 40 patients during treatment and follow-up are shown in Table 4. The most common toxicity was leukopenia. Grade 3 or higher leukopenia and granulocytopenia occurred in 26 and 19 patients, respectively. Grade 3 or higher thrombocytopenia and anemia occurred in 18 and 14 patients, respectively. Grade 3 or higher diarrhea occurred in 11 patients. Significant increase of neutropenia and diarrhea was noted in patients with three cycles of chemotherapy compared to those of one or two cycles ($p < 0.05$). There was no treatment-related death. We experienced two cases of Grade 3 of urinary bladder and six Grade 2 of the rectum regarding to late adverse event. No patients developed with Grade 3 or higher of late rectal toxicity. Late toxicity of the rectum and bladder showed no significant difference between patients with three cycles of chemotherapy and those with one to two cycles.

Comparison of historical control group

Between 1986 and 1998, we treated 43 patients with radiotherapy alone who were thought to be eligible for this protocol criteria using staging workup including MRI. During this period, systemic chemotherapy is not generally planned in our institutes; the majority of patients visited during this period were recruited in this cohort. In addition, MRI study was routinely performed to evaluate tumor volumetry in this period. This group (*historical control group*) was compared with the ALCRT group. Patient's characteristics of both groups were summarized in Table 5. Age and radiation dose of the historical control group proved to be significantly higher compared with those of ALCRT ($p < 0.05$). Stage distribution and tumor size did not show a significant difference between the two groups, although tumor size of ALCRT group had a slightly larger than that of the historical control group. ALCRT group showed a tendency for larger ratio of patients with positive lymph node compared with that of the historical control group ($p = 0.07$).

OAS and PFS showed a significant improvement in ALCRT group by univariate analysis. The 5-year OAS rate of ALCRT group is 78.8% (95%CI, 65.6–92.1%) and that of the historical control group is 48.8% (95%CI, 33.9–63.8%; $p = 0.02$, Fig. 2). The 5-year PFS rate of ALCRT group is 66.5% (95%CI, 51.4–81.6%) and that of historical control group is 37.2% (95%CI, 22.8–51.7%; $p = 0.006$, Fig. 3).

Table 5. Patient characteristics of both protocol group and historical control group

Factor	Protocol group	Historical control
Age (median: y)	54*	67
Size (median: mm)	61	55
Pelvic radiation (mean: Gy)	53.6**	59.2
Stage III-IV (%)	65	69.8
Lymph node–positive (%)	62.5***	42.9

* $p < 0.0001$.
** $p = 0.017$.
*** $p = 0.07$.

In multivariate analysis, ALCRT also showed a significant reduction both death and disease progression (Table 6). Hazard ratio of the ALCRT group was 0.639 (95%CI, 0.41–0.96; $p = 0.03$) in OAS and 0.534 (95%CI, 0.35–0.81; $p = 0.002$) in PFS. Late adverse event according to bladder and rectum showed no significant increase in ALCRT group compared with those of historical control group ($p < 0.05$).

DISCUSSION

To the best of our knowledge, this is the first report of successful outcome of chemoradiotherapy using extended-field radiotherapy. The OAS and PFS rates at 5 years were 78.8% (95%CI, 65.6–92.1%) and 66.5% (95%CI, 51.4–81.6%), respectively. Our results of OAS and PFS are thought to be quite comparable to the reported data of concurrent chemoradiotherapy (5, 6, 19) (Table 7). Our protocol has shown acceptable treatment compliance without increasing late toxicities with relatively long follow-up (median, 61.8 months). In addition, our cohort has a higher proportion of both advanced clinical stage and lymph node involvement including para-aortic region compared with reported data (1, 5, 6, 19).

We believe dynamic conformal radiotherapy have a benefit to reduce toxicities especially for chemoradiotherapy setting

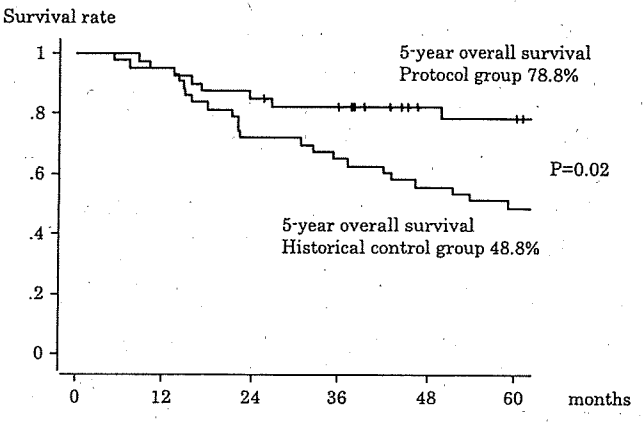

Fig. 2. Overall survival curves of groups of protocol treatment and historical control.

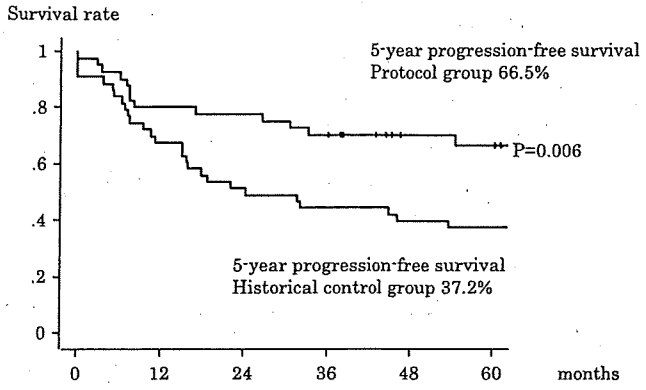

Fig. 3. Progression-free survival curves of groups of protocol treatment and historical control.

with large treatment volume such as extended-field radiotherapy (15, 20, 21). In many reports, researchers used a contiguous field technique for extended field treatment (22–26). This method had an advantage in a short treatment period and an accurate treatment volume. Sequential method such as ours is thought to have a deficit in longer treatment time and would have a potentially loss of disease control. Although patient number was small ($n = 5$), all patients with positive para-aortic disease are well controlled in our protocol. Thus we believe no apparent clinical disadvantage as to sequential radiotherapy for pelvic and para-aortic irradiation. There is another problem of sequential method as to field matching. Both pelvic and para-aortic field should be arranged carefully, because a gap between two fields had a potential risk of underdose or overdose. In this report, we did not experience both regional failure on gap area and late toxicity from excessive dose by overlapping. We also have reported acceptable outcome using sequential EBRT for para-aortic region in definitive and postoperative intent (15, 27). In these reports, para-aortic field was treated with four-field technique (27) or dynamic conformal radiotherapy (15) in sequential setting. In fact, many reports have failed to improve clinical results by simultaneous extended-field chemoradiotherapy (22–24). RTOG 0116 recruited patients with cervical carcinoma and high common iliac or para-aortic metastasis (22). Patients received extended contiguous field radiotherapy up to 54–59.4 Gy with concurrent administration of 40 mg/m^2 of weekly cisplatin. A total of 26 patients were entered, and

Table 6. Mulivariate analysis of several prognostic factor regarding to overall and progression-free survival

	Overall survival		Progression-free survival	
Factor (reference group)	Hazard ratio	p-value	Hazard ratio	p-value
Age (<62 y)	0.922	0.664	0.927	0.684
Stage (I–II)	1.10	0.600	1.073	0.673
Size (<60 mm)	1.10	0.597	1.409	0.049
Lymph node (no)	1.12	0.597	0.857	0.336
Modality (CRT)	0.639	0.031	0.534	0.0024

Table 7. Comparison clinical results of chemoradiotherapy with or without extended-field radiation

Author	Number	5-year survival	Toxicity (Grade 3 or more)
Varia	95	39 (3 y)	37.7
Grigsby	30	29 (4 y)	80
Maltefano	13	69	0
podczaski	33	31	6
Small	26	60 (18 months)	40
Present	40	78	5
chemoradiotherapy without extended field radiotherapy			
GOG85*	177	NS	4
GOG120			
Weekly CDDP	192	70	2.7
CDDP+5FU*	191	70	0.9
RTOG9001	193	73	13

Abbreviations: GOG = Gynecologic Oncology Group; CDDP = cisplatin; NS = not stated; * = same chemotherapy regimen; RTOG = radiation therapy oncology group.

developed 40% of late Grade 3/4 toxicity, including 8 patients requiring surgical intervention. Estimated OAS at 18 months was 60%. The majority of failure of these studies was based on low compliance from acute or late severe gastrointestinal toxicity. These reports also could not acquire comparable clinical results with standard chemoradiotherapy (22, 24). We reported promising clinical efficacy without increasing toxicity, so we believe sequential para-aortic irradiation should be taken into consideration in practice.

As for method of chemotherapy, cisplatin is now widely accepted as standard care for chemoradiotherapy for cervical cancer (2, 4, 6, 19). The GOG 120 study compared with definitive radiotherapy and hydroxyl-urea and concurrent chemoradiotherapy with cisplatin (6). In the GOG 120 study, two chemoradiotherapy arms were applied—such as weekly cisplatin and combination of 5FU and cisplatin (same arm of GOG 85). In recent report, there was no apparent benefit of addition of 5FU within both two arms, although dose of cisplatin varied much (100 mg/m^2 for the combined arm vs. 240 mg/m^2 for the weekly arm). In the RTOG 9001 study, 5-FU and cisplatin were used with concurrently in chemoradiotherapy arm. The sum of cisplatin of RTOG 9001 study was 225 mg/m^2. RTOG 9001 reported a subset analysis for Stage IB-II versus III-IV, statistical significance only for Stage IB-II subset was noted, leading some to suggest that chemoradiotherapy was not effective in more advanced disease stage (28). The update of RTOG 9001 demonstrated that, because the early stage of disease accrued to the protocol, a strong trend only was noted in the patients with more advanced disease (Stage III-IV) (5). Among three studies (GOG 85, GOG 120, RTOG 9001), the ratio of Stage III-IV disease ranged from 30% to 53.8%, and that of positive lymph node was 12.5–24%. In our cohort, the ratio of both advanced stage disease (III-IV: 65%) and positive lymph node was larger ratio (62.5%) compared with those reported study (4, 6, 19).

One of the reasons of our successful result regardless worse prognostic population of our ALCRT experience was sufficient dose intensity of systemic chemotherapy.

This method had an advantage of intensive drug administration because of minimizing acute toxicities, especially for mucosa and intestine; therefore, patients having potentially distant microscopic disease are thought to be better candidates for ALCRT. In previous report, major failure site of patient with Stage III disease in our institute was distant metastasis (12, 20), then we believe our treatment protocols are promising, especially for advanced disease and extended lymph node involvement with potentially hazards of para-aortic region. Using the ALCRT method, we could achieve high-dose administration (1.4 times higher than domestic standard dose of NDP) of a multidrug agent with successful compliance without increasing toxicity.

Finally, we have used NDP, the derivatives of cisplatin developed in Japan. This antitumor agent had a promising activity for cervical cancer (7, 8) and less toxicities of renal and gastrointestinal (29). We believe one of the reasons of our successful result of ALCRT was lower toxicity of NDP compared with cisplatin. In fact, our cohort showed no significant increase gastrointestinal toxicity and could archive a acceptable compliance of protocol compared with reported data using cisplatin (22). Again we should emphasize our reported effective outcomes of ALCRT with NDP for other malignancies (14, 30).

Our protocol seemed to have a promising advantage for patients with advanced disease or positive lymph node patients. However, this study has a definite limitation because of the retrospective comparison to historical matched control group. The several biases regarding patient selection and treatment content should be considered. In addition, our historical control group received radiotherapy alone, which was not present standard care.

But we believe that an acquired result of ALCRT was quite comparable, slightly better (78% vs. 70–73% in 5-year survival; Table 7) than those of standard chemoradiotherapy without para-aortic irradiation. Compared with their reported data, we should emphasize that our cohort had worse prognostic factors. To evaluate clinical efficacy of ALCRT, especially for more advanced disease or positive lymph node, properly randomized controlled trial comparing ALCRT with NDP with concurrent chemoradiotherapy using cisplatin should be tested in the future.

CONCLUSION

Using both dynamic conformational technique and ALCRT setting, extended-field radiation therapy could be successfully combined with intense multiagent chemotherapy. ALCRT is thought to significantly reduce both recurrence and mortality of patients with advanced cervical carcinoma, chiefly with Stage III or positive lymph nodes. We believed that our promising data of the Phase II study warranted advancing to Phase III study comparing ALCRT with NDP to standard concurrent chemoradiotherapy using cisplatin.

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特集 乳癌診療と教育：次世代への期待

放射線療法

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The main goal of adjuvant radiation therapy is to eradicate residual disease thus reducing local recurrence and improving survival rate. Radiation therapy is regularly employed after breast-conservation surgery. Shorter hypo-fractionation schemes achieve comparable results to standard fractionation schemes. A further radiation boost is commonly given to the tumor bed. The new strategies such as accelerated partial breast irradiation are under investigation for selected patients in breast-conservation setting. Postoperative chest wall and regional lymph node radiation therapy has traditionally been given to selected patients considered at high risk for local-regional failure following mastectomy. Radiation therapy can decrease local-regional recurrence in this group, even among those patients who receive adjuvant chemotherapy. Delaying radiation therapy for several months after surgery until the completion of adjuvant chemotherapy appears safe and may be preferable for patients at high risk of distant dissemination. The rate of second malignancies following adjuvant radiation therapy is very low.

Key words：Breast cancer, Radiation therapy
Jpn J Breast Cancer 24(special number)：47～53，2009

はじめに

乳癌に対する放射線療法については，多数の論文から厳選されたエビデンスを総括した日本乳癌学会のガイドラインや放射線治療計画ガイドラインの他に，多数の教科書にて記載が充実している．このため標準治療として国内で最も確立されている放射線療法であると考えられてきた．厚生労働省がん研究助成金「井上班・手島班・光森班」による経年的臨床実態調査：patterns of care study（PCS）の結果では，各種ガイドラインの発行などにより着実な日常診療の改善が認められるものの，一部に問題があることが示された．

1．診療の最近の進歩

1）乳房温存療法における術後放射線療法は局所制御だけでなく生存に関して有益である

乳房温存手術後の乳房照射の有用性は，10の臨床試験に登録された7,311症例を分析したEarly Breast Cancer Trialists' Collaborative Group（EBCTCG）による2005年のメタアナリシスによって証明された[1]．温存手術後に放射線治療を加えることにより，局所再発は70％減少し，15年での死亡の絶対リスクが5.4％減少することが示された．放射線治療により乳房内再発を4件予防することにより1件の乳癌死を予防できると見積もられている．術後療法として内分泌化学療法だけでは局所制御効果は不十分であり，放射線療法により乳房内再発率の有意な減少がみられる[2]．乳房温存療法後の局所再発の危険因子は，切除断端陽性，若年患者（35歳あるいは40歳以下）があげられる．

2）乳房切除術後放射線療法（PMRT）は局所制御だけでなく生存に関して有益である

乳房切除術照射は局所再発減少と死亡絶対リスク減少の有用性があることが，メタアナリシスから示された．EBCTCGメタアナリシス（8,505例）の結果から，5年局所領域リンパ節再発率を23%から6%に減少させることが証明され，36のランダム化比較試験のメタアナリシス（13,199例）結果でも，局所領域リンパ節再発の相対危険率を70～80%減少させた[1, 4]．局所領域リンパ節再発の危険因子としては，4個以上の腋窩リンパ節転移陽性例，原発巣の大きい患者（5 cm 以上），深部断端陽性例などである[5]．

3）局所（胸壁・領域リンパ節）再発に対する救済放射線療法

乳房切除術後の胸壁再発やリンパ節再発は，多様な病態を呈し，遠隔転移を伴うことがまれでない．乳房切除術により長期間に無病であった後の限局性胸壁再発は期待生命予後が長いので，再度の長期間無病状態を目指して積極的に救済治療することが推奨される[6]．

4）遠隔転移（骨・脳・肺・他）に対する緩和目的の放射線療法

メタアナリシスでは，骨転移の疼痛緩和に対する線量－効果関係は明らかでない[7]．骨融解性病変が高度で比較的長い予後が期待される場合は分割照射法が推奨される．1回照射と分割照射を比較した最近のメタアナリシスでは前者において同一部位への再照射率が高く，病的骨折が高くなる傾向があるものの，両者間に全寛解率や完全寛解率に差がみられない点では一致している[7, 8]．放射線治療と高用量ビスフォスフォネートを併用すると疼痛緩和だけではなく，画像的に骨硬化もみられる．ストロンチウム－89によるアイソトープ治療については日本でも多施設共同オープン試験が行われ，疼痛尺度と鎮痛剤使用量を組合せた有効率は46%であった．投与後8週ころに血液毒性がnadirとなるため，化学療法の継続または予定されている患者への適応には慎重を要する．

1～4個の脳転移を対象とした臨床試験が行われ，全脳照射に定位手術的照射を追加する意義が示された[9, 10]．JROSG99-1では定位手術的照射単独ではなく，全脳照射を併用する方が局所制御割合が高いことが示された[11]．

2．現在の研究の焦点は何か

1）放射線療法の適応に関する研究

（1）乳房温存術後乳房照射は全員に必要か？

局所再発のリスクが少なく放射線療法を省略できる群を同定する研究や，切除断端陰性（取りきれたこと）の保証をする研究が実施されている．腫瘍が小さいほど，手術の切除範囲が大きいほど，患者の年齢が高いほど，放射線療法は省略できる可能性があると考えられる．4つのランダム化比較試験において，放射線療法を省略できるデータは示されていない[12, 13]．エストロゲン受容体陽性の70歳例では，内分泌療法を行えば，放射線療法を省略できるかもしれないという意見もある．国内でも局所再発リスクが少なく放射線治療を省略し得る群を同定する臨床試験が実施されている．今後も，真に放射線療法を必要とする患者を同定する努力を続けるべきであろう．

（2）乳房切除術後照射：PMRTの適応は？

腋窩リンパ節転移1～3個の患者に関するDanish 82b+82c Trialの解析結果は，PMRTにより局所領域リンパ節再発の抑制効果と生存率の向上（15年生存率相対リスク17%改善）が示された[14]．この群の全患者にPMRTを行うべきか，幅広い合意はいまだ得られていない．摘出リンパ節中の転移リンパ節の割合（nodal ratio）が高いほど局所領域リンパ節再発率が高いことが報告され，局所領域リンパ節再発の高リスク患者を見出しPMRTが必要な患者を同定する研究が続けられている．

2）放射線照射法に関する研究

（1）加速乳房部分照射への期待

MILAN Trial・NSABP-B06 など4つの臨床試験において，非照射群の同側乳房内再発のうち腫瘍床近傍での発生は70～86%であった[15]．近傍以外再発の低リスク群に限れば，腫瘍床近傍に限局した部分照射でも十分と考えられる．術後照射を短縮できれば，患者や家族・職場への負担が減る．欧米では，1990年代の第 I/II 相試験を経て，第 III 相試験が行われている．方法には，外照射3-D CRT（IMRT），バルーン法，組織内照射などがある．現在，わが国でも施設間における技術的な再現性を確立する必要があることから，多施設共同 feasibility study が開始された．

（2）乳房切除後の術後照射における強度変調放射線療法（IMRT）の応用

米国では強度変調放射線療法（IMRT）が，急速に日常診療に普及してきている．従来の3次元原体放射線療法（3-D conformal radiation therapy）では，実現不可能であったリスク臓器（肺・心臓・脊髄など）の線量低減が可能になり，標的体積（planning target volume）に有効な治癒線量を処方できるようになった．本邦では，乳癌に対する IMRT の応用は進んでいない．

3）分割照射に関する研究

短期全乳房照射の利便性

乳癌患者には有職者や育児年代も多く，5～7週間の通院が本人・家族や職場への負担となりやすい．米国でも自宅から放射線治療施設までの距離に反比例して放射線療法の実施率が低くなると報告されている．こうした患者には，治療期間を短縮することが望ましい．カナダで行われたランダム化比較試験では42.5Gy/16回/22日と50Gy/25回/35日が比較され，両者の5年局所再発率，無病生存率に差を認めなかった[16]．また，イギリスで行われた50Gy/25回/5週，42.9Gy/13回/5週，39Gy/13回/5週の3者を比較したランダム化比較試験では，同側乳房内再発率に関して，50Gy/25回と42.9Gy/13回の間には有意差はなかったが，39Gy/13回は同側乳房内再発率がやや高く，42.9Gy/13回/5週と39Gy/13回/5週の間には有意差があったとしている[17, 18]．至適な線量・分割についてはイギリスで現在進行中のランダム化比較試験の結果が待たれる．

4）照射線量に関する研究

全乳房照射に引き続くブースト照射線量

病理学的な断端陽性症例では断端陰性症例に比べて局所再発率が高い．病理学的な断端陰性症例については腫瘍床に対する10～16Gy のブースト照射が乳房内再発のリスクを減少させる．EORTC22881－10882トライアルでは，同側乳房内再発抑制効果はすべての年齢層において有意に減少した．EORTC では，年齢別にブースト照射線量を設定して臨床試験中である[19]．断端の判断や切除範囲の異なるわが国の実臨床において，ブースト照射が同様の利益をもたらすかどうかについては独自の検証が必要である．

5）放射線毒性を軽減する研究

心臓の被曝照射線量低減の試み

初期の臨床試験では，放射線照射群で有意に心疾患による死亡が増加したと報告された[20, 21]．心臓への吸収線量を減らすために，胸骨傍リンパ節や胸壁には電子線を用いた方法や，呼吸同期照射・呼吸管理化照射の研究が行われている．

6）再発に対する救済治療の研究

乳房温存療法後の乳房内再発については，一次治療にて乳房照射されている場合が多く，乳房切除術が推奨される．再温存療法の研究も行われている[22]．

3．次世代に期待するもの

1）ガイドライン：ボトムラインの理解

現在の研究の焦点は，乳癌学会のガイドラインにて推奨レベルが低い内容や，不明であるとされてい

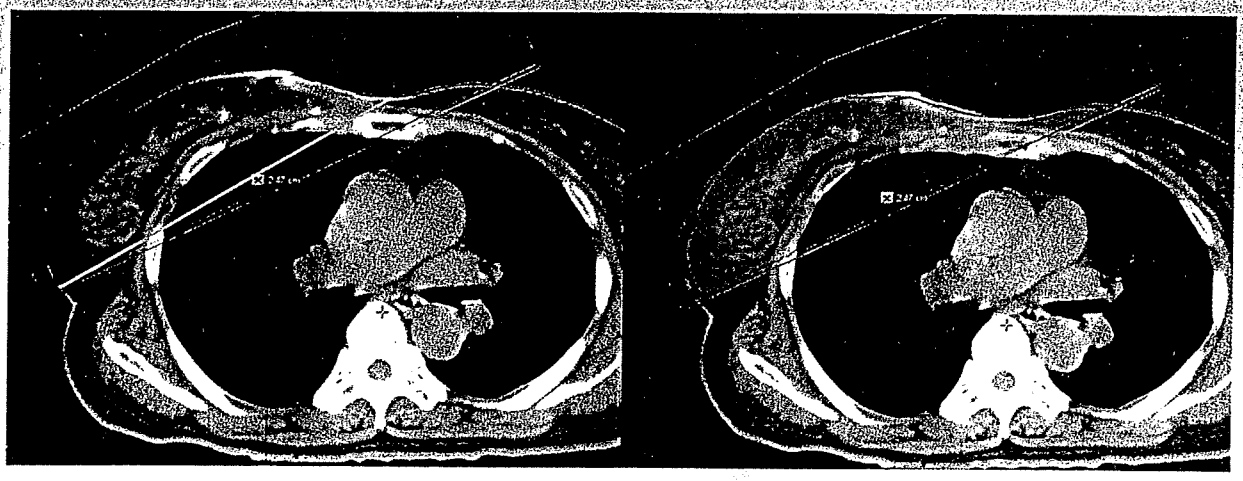


図1　内側（A領域）例におけるクリップの位置と乳房温存術後の高濃度域と線量分布図

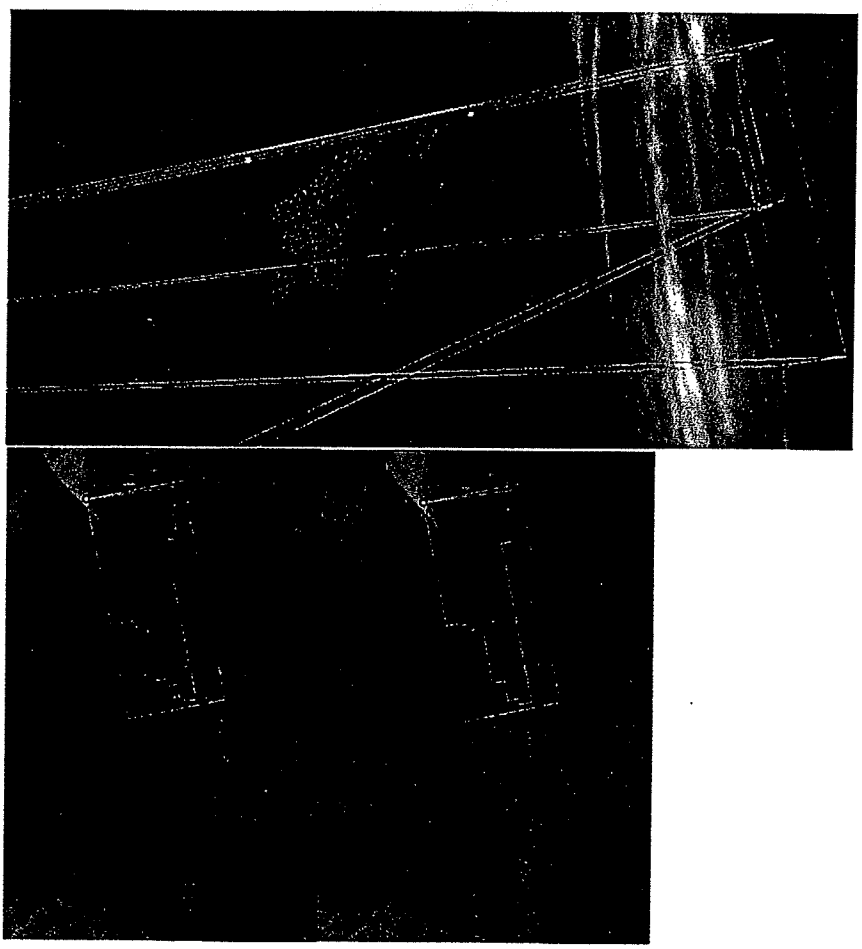
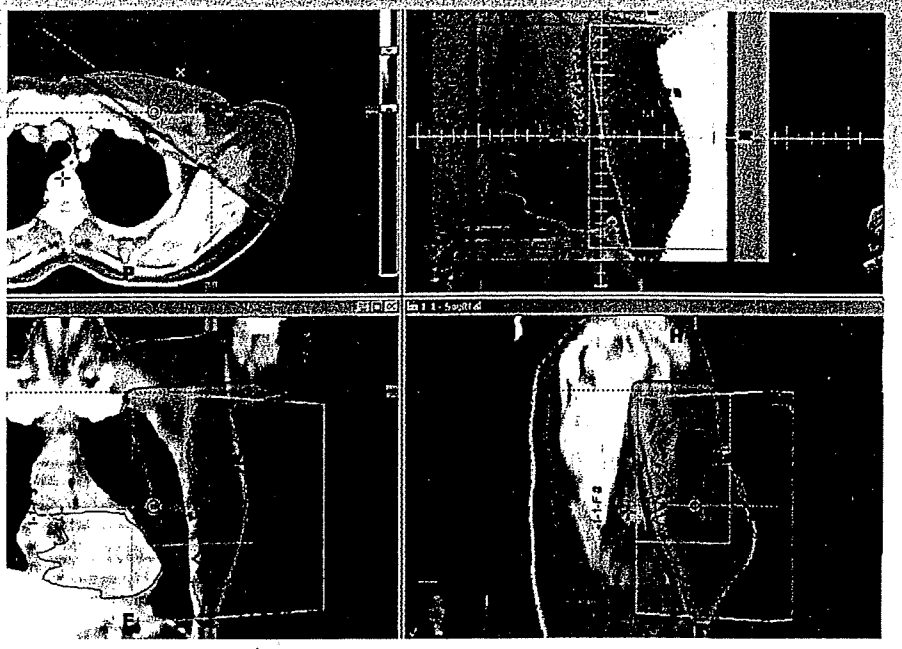


図2　腋窩例における治療計画図と Field with in Field 法の線量分布図

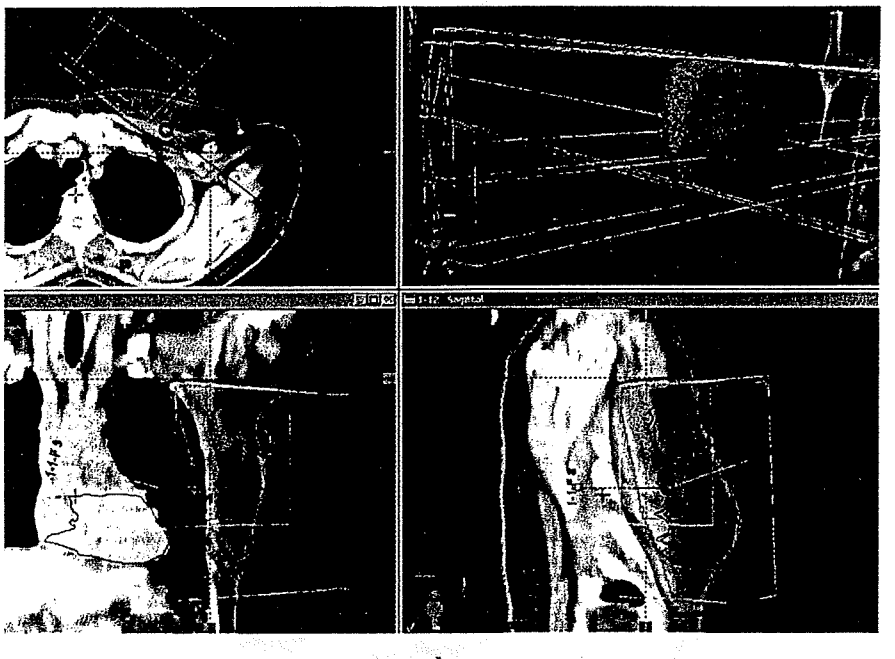
ることであろう．そのすべてについて臨床研究が行われているが，臨床試験の実施可能性や解決すべき優先順位の問題から，問題解決が先送りされているものもある．ガイドラインをよく理解することが，重要と思われる．

2）応用力：柔軟性と科学的判断

ガイドラインを元に，放射線治療計画に配慮を要する場合について，自験例を述べる．乳房温存術後照射照射範囲としては，内側は正中，外側は中（外）腋窩線，上縁は鎖骨下縁，下縁は乳房より1～2cm下方までを含めるようにすることが標準的である．しかし，内側（A領域）例・頭側例・腋窩に近い例・高度肥満例・腕があがらない例・対側照射例では配慮が必要である．



a



b

図3　上肢挙上困難例における治療計画図
a：通常の方法
b：療寝台を廻した方法

（1）内側（A領域）例に対する配慮

原発巣が内側に位置する例では，ガイドラインに従って胸骨正中線と中腋窩腺を基準に，黄色の線のように治療計画を立てると，部分摘出術病巣部位は，照射野の辺縁となり治療線量を投与できない場合もある（図1左）．この例では，部分摘出術病巣部の線量を処方照射線量の95％以上にするために，反対側乳房に一部かかることを患者にも説明し，了解を得て図1右のような線量分布図を立案し，放射線治療を行った．

（2）頭側例・腋窩に近い例

腋窩に近い例では，治療寝台を健常側に振り，腋窩部に十分な線量を処方することが可能である（図2）．

胸壁上部は厚く低線量域になるので，Field with in Field 法で追加照射を行うことが必要であった．

3）腕があがらない例

腕があがらない例では，上肢挙上のリハビリを励行し設定を遅らせるが，治療寝台を廻した方法を用いることで解決できる場合もある（図3）．

4．教育の在り方と，学び方，専門医になるには

がん診療拠点病院が指定されたものの，放射線治療部門の整備が進められた施設は一部であり，治療機器整備や人的資源の確保に関しては課題が山積している．特に絶対的に不足している放射線治療専門医・放射線治療専任技師・放射線物理士を育成するための教育制度が，早急に構築されることを希望する．

腫瘍外科医・腫瘍内科医が，基礎研修中に放射線治療の経験を積むことは，相互理解のために貴重な経験となろう．

まとめ

放射線療法による治療効果を最大限に生かし，不利益を最小限にするために，最適な科学的判断をして，最適な照射技術を日々の診療で実践する必要がある．近年，Multi-disciplinary conference や Cancer board が活動している施設では，医療者が放射線治療を学習する機会が増えつつあり，放射線腫瘍学の知見を生かしつつ，広い視点から慎重に decision making することができるようになりつつある．白熱した議論の中から生まれた shared decision は，患者だけでなく医療者にとって大変重要である．

謝辞

本稿が，乳癌診療に志を持つ医療者，特に若手外科医にとって，放射線療法の現状と問題点について理解を深め，将来の研究の方向性を探る一助になれば幸いである．

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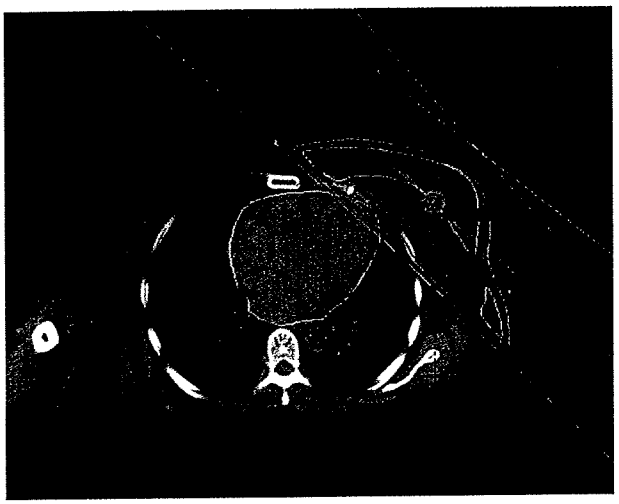

図1　全乳房を含めた接線照射

は局所制御の改善のみならず，生存率の向上にもつながることが示されている[2]．しかし，不適切な照射技術は治療成績の向上が得られないだけではなく，毒性による死亡率の増加にもつながるため，放射線治療に携わる医療者は適切な照射技術を身につける必要がある．

1．乳房温存療法における術後放射線療法

1）適　応

原則として，乳房温存を目的とした部分切除術が施行された症例すべてが術後照射の適応となる．海外ではHarvard Joint Centerをはじめとするいくつかの研究グループにより放射線治療を省略できる集団を見い出す試みが行われたがすべて失敗に終わった．一方，国内の限られた施設では，術後放射線照射を省く乳房温存療法の臨床研究が実施されている．放射線治療の絶対的非適応は，妊娠中の女性と患側乳房への照射歴がある症例であり，相対的非適応としては背臥位にて患側上肢を挙上できない症例や膠原病（強皮症や全身性紅斑性狼瘡）を有する症例である[3]．膠原病における放射線治療の安全性に関しては十分なエビデンスがなく不明な点が多いが，組織壊死や肺障害が出現するとの報告があり十分に注意が必要である．乳房温存術を行う際には，事前に膠原病の合併がないことを確認しておく必要がある．また，ホルモン感受性を有する70歳以上の高齢者の場合，放射線療法を省略しても乳房内再発率の増加はわずかであり死亡のリスクはほとんど増加しないと考えられており，状況によっては放射線治療を省略することは許容される[4]．

2）全乳房照射

乳房温存術後の乳房照射の有用性はこれまで複数のランダム化比較試験とそれをまとめたメタ解析により確認されている．通常，患側乳房全体を照射野に含め4～6 MVのエネルギーの低いX線を用いて50Gy/25分割/5週間前後の照射（追加照射として10～16Gyが投与されることもある）を行う．メタ解析の結果，術後照射を行うことで乳房内再発が1/3に減少し，非照射に比べ死亡の絶対リスクが5.4%改善することが示されている[2]．

照射範囲としては，内側は正中，外側は中（外）腋窩線，上縁は鎖骨下縁，下縁は乳房より1～2 cm下方までを含めるようにする．肺や心臓への線量を可能な限り減らすため接線照射法が用いられる（図1）．肺や心臓などのリスク臓器への線量，また患側乳房内の線量の均等性を客観的に評価するため，Dose-Volume-Histogram（DVH）を用いる（図2）．胸郭の変形があり心臓が極端に前面に張り出している症例ではこの照射範囲を忠実に守ると，心臓が広範囲に照射されることになり注意が必要で

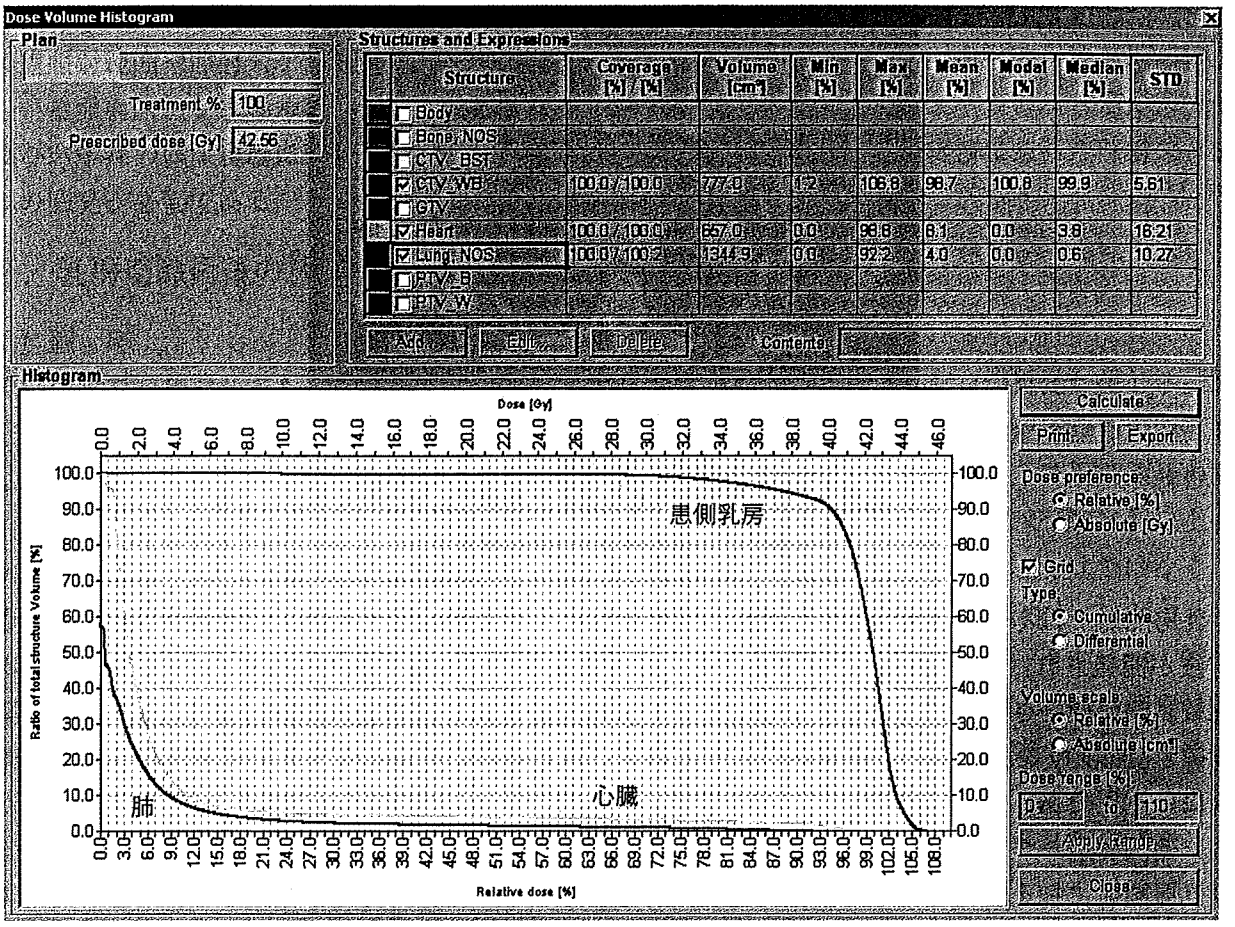

図2　Dose-Volume-Histogram (DVH)
血線量－容積の関係をヒストグラムで評価する.

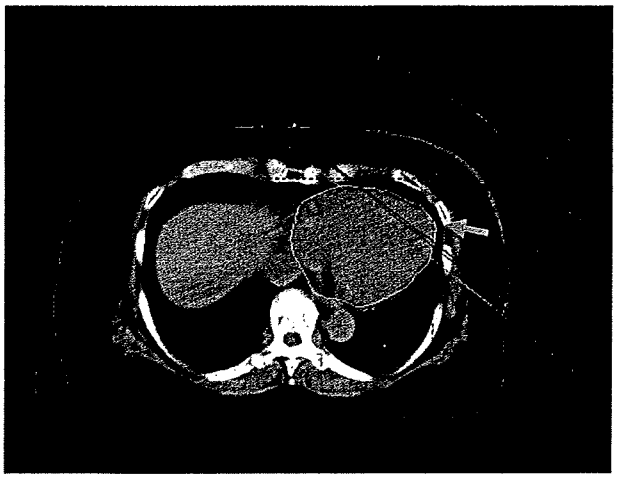

図3　乳房接線照射
心臓の一部が照射野の中に含まれていることに注意.

ある（**図3**）. 私見ではあるが, このように胸郭の変形がある症例では内側原発の場合には照射野外側縁を中腋窩線よりやや上方にずらし, また外側原発の場合には照射野内側縁を正中よりやや外側にずらすことで照射野から心臓をはずす工夫をするとよい. 乳房切除術後の詳細な病理の検討から, 原発巣から離れるほど癌細胞が残存する可能性が下がることが示されており, このような方法を行っても乳房内再発の増加は招きにくいと考える.

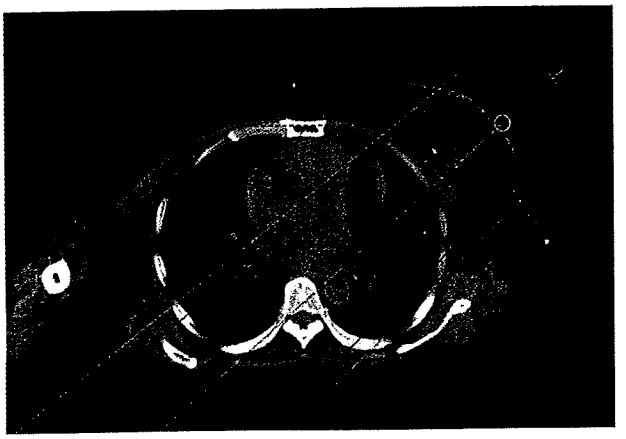

図4　電子線照射
皮膚近傍から胸筋前面までが主に照射される.

全乳房照射ではあるが通常の5～6週間の照射ではなく，1回線量をあげ，短期間で照射を終了させる方法が開発され，安全性および有効性ともに通常照射法の場合と同等であることが2つのランダム化比較試験で検証された[5,6]．カナダのランダム化比較試験では1回線量を2.66Gyとし16回（約3週間）で総線量42.56Gyを投与する方法が採用されており，遠方からの通院患者や高齢で頻回の通院が困難な場合には有用である.

3）追加照射

全乳房照射に加え腫瘍のあった部位に追加照射を行うことで乳房内再発を軽減させることが2つのランダム化比較試験で示された[7]．ヨーロッパのグループの報告では，追加照射により乳房内再発が10.2％から6.2％に減少し，乳房内再発のハザード比も0.59に低下することが示された．全年齢層で乳房内再発のリスクが低下するが，特に50歳以下の症例でのリスク減少幅が大きい．これらの臨床試験は海外で行われたものであり，病理診断による切除断端の評価は本邦の実情とは異なるため，この試験の結果をわれわれの臨床の現場に持ち込む際には注意が必要である．本邦では切除標本を全割して詳細に観察し，切除縁から腫瘍細胞までの距離が5 mm以上の場合を切除断端陰性と診断している施設が多く，欧米のような切除縁周囲のみを評価し切除面に腫瘍細胞の露出がない（または2 mm以内）場合を切除断端陰性としている状況とは大きく異なる．追加照射には小線源や電子線を用いるが，一般臨床では電子線を用いて10～16Gy/5～8回程度が追加されることが多い．電子線は質量を持つ放射線（荷電粒子）であり，体内に入るとエネルギーを失うため，X線と異なり体内の深部に入りづらい性格を有する．適切な電子線のエネルギーを選択することで2～5 cm程度の深さまでが治療領域となる（図4）．しかし，一部ではあるが肺や心臓へも照射されるため注意が必要である.

4）加速部分照射

乳房温存療法における乳房内再発の形式を検討すると，約70～90％の再発が腫瘍床近傍から生じることが報告されている．乳房全体を放射線治療の標的とするのではなく腫瘍のあった部位のみを標的とし，照射範囲を小さくすることで正常組織の耐容線量が上がり，1回線量を3.4～6 Gy程度まで上げ，1～2週間で照射を終了させるという照射法の開発が進められている[8]．照射方法は，小線源とカテーテルを用いた組織内照射，小線源とバルーンを組み合わせた方法，電子線や表在X線を用いた術中照射，通常のX線を用いた三次元外部照射法などがある．現時点では試験的治療として位置付けられており，有効性や安全性に十分配慮した臨床試験を計画して行うべきである．これまでの短期経過観察では安全性は高いとする報告が多かったが，最近，組織内照射や，バルーンや三次元外部照射法を用いた方法でも比較的早期に許容しがたい乳房の変形や脂肪壊死の報告が散見されるようになり，十分な注意が必要

である[9].

至適照射範囲や照射スケジュールは確立しておらず今後の研究課題である．現在欧米で最も多く行われている照射スケジュールは1週間で10回照射（1日2回照射）するスケジュールであるが，スタッフの少ない本邦の臨床現場には導入しにくい照射スケジュールであり，本邦の実情にあった照射スケジュールの開発が必要である．

2．乳房切除術後の放射線療法

1）適　応

乳房切除術を施行しても一部の症例では胸壁再発や鎖骨上窩などの領域リンパ節再発が生じる．胸壁再発が最も多く，続いて鎖骨上窩リンパ節領域からの再発が続く．胸骨傍リンパ節領域からの臨床的再発は少なく術後照射の際に同部位を含めるべきかに関しては議論が分かれる．現在，乳房切除後の放射線治療の適応に関してコンセンサスが得られているのは，病理学的に腋窩リンパ節転移が4個以上ある症例である．3つのランダム化比較試験により局所－領域リンパ節再発が1/3に減るだけではなく，生存率も向上することが示されており，本邦の診療ガイドラインでも術後照射が推奨されている[3]．米国の診療ガイドラインNCCNでは腋窩リンパ節転移1～3個の症例にも術後照射を行うよう強く推奨されているが，科学的根拠となる信頼性の高いエビデンスは少ない．T3N0症例やT1～2N0症例やリンパ管浸潤例などにも術後照射が必要となるかを検討した遡及的報告が散見されるが一定の見解はなく今後の研究課題である．

また，術前化学療法を施行し乳房切除後の病理学的所見で腋窩リンパ節転移が1～3個認められた場合に術後照射の適応となるかに関しては統一した見解はないものの，化学療法を施行していなければ腋窩リンパ節転移が4個以上であった可能性が高いこと，術前化学療法によく反応した症例でも術後照射を省略した場合には局所再発率が高いこと，また術前化学療法非施行例でも腋窩リンパ節転移が1～3個の症例に対しても術後照射をすべきとの見解もある[9]．

2）照射方法

患側胸壁に加え患側鎖骨上窩リンパ節領域を照射野に含める．胸壁照射は前述の乳房照射と同様に接線照射法で行われる．乳房照射と同様に50Gy/25回/5週間程度の照射が行われる．照射の標的となる皮膚表面近傍の線量を高めるためボーラス材を用いることもあるが，その必要性に関しては一定の見解はない．切除断端陽性例に対しては追加照射として10～16Gyが投与される．この際にも電子線が用いられることが多いが，胸壁は厚みが薄いため肺や心臓に照射される線量が多くなることがあるので注意が必要である．鎖骨上窩リンパ節領域は脊髄をはずして斜め前方から照射するが，胸壁照射との接合面を正確に合わせることが重要である．Half-field techniqueやRod-chain techniqueなどの方法などがあるが物理学的な正確性が求められる．鎖骨上窩リンパ節領域の線量分布の均等性を上げるために背側から同領域へ照射を追加することがあるが，良好な線量分布はあまり得られていないとの報告もあり臨床的意義も明らかではない．

胸骨傍リンパ節領域を含めるべきかに関しては議論が分かれる．特に左側の場合には心臓への照射が問題となるため胸骨傍リンパ節領域を照射野に含める際には十分な注意が必要である．具体的な方法としては呼吸同期システムを用いて肺や心臓への線量を下げる方法や，胸骨傍リンパ節転移が多いとされる第1肋間から第4肋間までを照射野に含める（partial wide tangent field technique）などの試みがなされている．いづれにしても三次元放射線治療計画や呼吸同期システムなどの装置が必要であり，このような装置は安全に放射線治療を行うために用意されるべきものである．

3．局所再発における放射線療法

局所再発に対する治療には一定の見解が得られていない．通常，乳房温存療法後の乳房内再発には乳房切除術が施行されることが多い．乳房温存を強く希望される症例に対し再度部分切除術と照射を行った報告があるが，症例数の少ない遡及的報告であり長期の安全性に関する情報はなく注意が必要である．

乳房切除術後の胸壁再発に関しても標準的治療は存在しない．単発の局所再発例に対しては切除術が施行され術後照射が検討される．切除可能であった症例には50～60Gyの術後照射が，肉眼的に残存腫瘍がある場合には60～70Gyが投与される．しかし，これを裏付ける科学的根拠はなく，著者が訪問した米国の一部の施設で施行している方針でありコンセンサスが得られているわけではないが，可能な限り積極的な救済治療を行うことが一般的である．また，局所再発例の多くは全身転移を生じることが多く，再発が確認された時点では胸壁再発だけであっても遠隔転移が生じる可能性は高く，最終的予後は不良である．このため全身療法が施行されるが，放射線治療とのタイミングに関しても不明な点が多い．局所再発例は，初回治療時の病期，ホルモン感受性，年齢，再発までの期間などにより予後が大きくことなるため，一律に同様の救済治療が行なわれるべきではないと考えられる．信頼性の高いエビデンスはなく，従来は個々の医師の判断にゆだねられていた．近年，Multi-disciplinary conferenceやCancer boardが活動している施設では，広い視点から慎重にdecision makingすることができるようになった．

4．有害事象

急性期の有害事象として最も多いのは，照射部位に一致した放射線皮膚炎である．多くの場合軽度の皮膚炎であることが多く，Grade 2以上の皮膚炎が認められることは少ない．乳房が大きな症例では線量分布の不均等性や皮膚近傍の線量の増加から時にGrade 2の皮膚炎が生じることがある．皮膚炎により照射の休止が必要となることはまれであるが，より患者の負担を軽減して治療が受けられるよう，皮膚の保護などのケアを指導するとよい．

この他の照射期間中の有害事象としては，軽度の全身倦怠感や宿酔などの症状が出現するが照射を休止するほどのものはほとんどみられない．しかし，遠方からの通院患者や仕事を持つ患者の負担は必ずしも無視できるものではない．鎖骨上窩を照射野に含めた場合には咽頭痛が生じる．鎮痛剤の投与などの保存的対処法を行う．

放射線肺臓炎は約１％の症例で認められる．照射野に含まれる肺野の幅を最大で3 cm以下にすることでその発生頻度を低く抑えることができる．しかし，含まれる肺野の範囲の大小にかかわらず一部の症例で器質化肺炎（BOOP）が生じることが報告されており，全体の1.5％程度に発症する[10]．照射される肺野内のみならず照射されていない部位にも生じることがあり，その発生機序は不明である．発症は照射後１年以内であり，ステロイド投与により症状が改善することや一部の症例で再燃がみられることなどが報告されている．

この他の遅発性有害事象としては，肋骨骨折（１～２％）や腕神経叢麻痺（まれ）があげられる．腕神経叢麻痺は１回線量を2 Gyより高い線量を用いた場合や総線量が50Gyを超えた場合に生じる可能性が高くなるため，鎖骨上窩への照射を行う際には注意が必要である．メタ解析の結果から，心筋障害のリスクは非照射の場合の1.27倍，対側乳癌の発生リスクは非照射の場合の1.18倍となることが示されており，より毒性の低い照射技術の開発が望まれる[2]．

まとめ

乳癌における術後放射線療法について解説した．放射線療法による効果を最大限に上げ，不利益を最小限にするため適正な照射技術を日々の診療で生かす必要がある．ただし，現在の三次元的放射線治療