A Survey of Patients with Inflammatory Skin Recurrence Corresponding to the Area of Previous Irradiation after Postoperative Radiotherapy for Breast Cancer

Kayoko TSUJINO[1]*, Kenichi KASHIHARA[2], Shouko KOTANI[3], Kazushige HAYAKAWA[3], Kazufumi IMANAKA[4], Yasuhiro TAKADA[5], Takashi UNO[6], Hideki HIRATA[7], Yuko KANEYASU[8], Kenji SEKIGUCHI[9], Etsuyo OGO[10], Junichi HIRATSUKA[11], Eisaku YODEN[1,11] and Toshinori SOEJIMA[1]

Breast cancer/Local recurrence/Postoperative radiotherapy/Inflammatory recurrence.

One of the unusual patterns of local recurrence in breast cancer patient is an inflammatory skin recurrence (ISR) sharply demarcating the area of previous radiation fields. To clarify the characteristics of this recurrence, we conducted a nationwide survey. We sent a survey to radiation oncologists at 200 institutions in Japan and received answers from 92. Of these, 24 institutions had some experience with patients who developed ISR affecting the previously irradiated area. The case details of 16 patients from 11 institutions were available and analyzed in this study. Eight patients experienced ISR after breast conservative therapy (groupA) and 8 patients experienced ISR after post-mastectomy radiotherapy (groupB). The postoperative pathological examination of groups A and B showed positive axillary lymph-nodes in 7/8 and 8/8 patients, positive lymphatic invasion in 4/7 and 7/8 patients, and ER status negative in 7/8 and 6/7 patients respectively. Median survival period was 266 days in groupA and 1105 days in groupB (p = 0.0001). Patients who developed the ISR tended to have several characteristics, including positive lymph-node metastases, intensive lymphatic invasion, and ER status negative. Physicians should contemplate the diagnosis of ISR next to radiation recall or radiation dermatitis, especially when the aforementioned risk factors are present.

INTRODUCTION

Loco-regional recurrences are common in patients with breast cancer who have been treated by breast conserving therapy (BCT) or radical mastectomy (RM).[1–3] An unusual

*Corresponding author: Phone: +81-78-929-1151,
Fax: +81-78-929-2380,
E-mail: tsuk@mub.biglobe.ne.jp
[1]Department of Radiation Oncology, Hyogo Cancer Center, 13-70 Kitaoji-cho, Akashi-city, Hyogo 673-8558, Japan; [2]Department of Radiology, Ehime Prefectural Central Hospital, Matsuyama, Japan; [3]Department of Radiology, Kitasato University School of Medicine, Sagamihara, Japan; [4]Department of Radiology, Nishi-Kobe Medical Center, Kobe, Japan; [5]Department of Radiology, Hyogo College of Medicine, Nishinomiya, Japan; [6]Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan; [7]Department of Health Sciences, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan; [8]Department of Radiation Oncology, Faculty of Medicine, Hiroshima University, Hiroshima, Japan; [9]Department of Radiation Oncology, St. Luke's International Hospital, Tokyo, Japan; [10]Department of Radiology, Kurume University School of Medicine, Kurume, Japan; [11]Department of Radiation Oncology, Kawasaki Medical School, Kurashiki, Japan.
doi:10.1269/jrr.11010

pattern observed with loco-regional recurrence is inflammatory skin recurrence (ISR), also known as carcinoma erysipeloides,[4] characterized by cutaneous metastatic carcinoma with lymphatic involvement. It sometimes occurs exactly and sharply matched to the area of previous postoperative irradiation and it mimics radiation dermatitis or radiation recall phenomenon. Postoperative radiotherapy appears to facilitate tumor recurrence in the area of previously irradiated skin. However, the mechanism and the characteristics of this recurrence are not well understood. We therefore conducted a nationwide survey to study the characteristics and prognoses of breast cancer patients with ISR corresponding to the previously irradiated area.

MATERIALS AND METHODS

Surveys regarding experiences with ISR corresponding to the previous radiation fields after BCT or postmastectomy radiotherapy (PMRT) were sent in February 2006 to radiation oncologists of the Japanese Society for Therapeutic Radiology and Oncology working at 200 certified institutes in Japan. Ninety-two institutes (46%) returned the completed

questionnaires. Of these, 24 institutes (26%) had some experiences with patients who had experienced ISR affecting the previously irradiated fields.

A second survey was sent to these 24 institutions regarding the characteristics and clinical courses of each patient. Of these, case details of 16 patients from 11 institutes were available. These 16 patients were analyzed in this study. All patients' information was submitted anonymously. After discussion between the authors, a third survey was sent later to the 11 institutions regarding population parameters of breast cancer patients treated with postoperative radiotherapy to estimate the approximate incidence of ISR. Because different time periods were used for the population parameters in the patient database of each institute, the third survey requested data regarding numbers of breast cancer patients treated with postoperative radiotherapy at each facility over the period from the oldest available year considered appropriate till 2005. The cumulative survival period was calculated using the Kaplan-Meier method and examined by the log-rank test (Dr. SPSS II, SPSS Japan).

RESULTS

Eight patients experienced ISR after BCT (group A) and another 8 patients experienced ISR after PMRT (group B).

Patient characteristics and postoperative pathology

Patient characteristics and postoperative pathological findings for the 8 patients in group A are summarized in Table 1. The age of the patients ranged from 42 to 86 (median, 61) years old. The postoperative histology showed positive axillary lymph nodes in 7 of 8 patients (more than 4 nodes in 4 of 8 patients), positive lymphatic invasion in 4 of 7 patients (extensive invasion in 3 of 7), negative ER status in 7 of 8 patients, and close or positive surgical margins in 3

of 8 patients. Postoperative radiotherapy was delivered to the conserved breast only in 5 of 8 patients, and to both supraclavicular region and breast in 3 of 8 patients. Adjuvant or neo-adjuvant chemotherapy was administered in 6 of 8 patients.

The group B patient characteristics and postoperative pathological findings are given in Table 2. Ages ranged from 38 to 67 (median, 56) years old. The postoperative histology showed positive axillary lymphnodes in 8 of 8 patients (more than 4 nodes in 5 of 8 patients), positive lymphatic invasion in 7 of 8 patients (extensive invasion in 4 of 8), negative ER status in 6 of 7 patients, and close or positive margin in 1 of 8 patients. Postoperative radiotherapy was delivered to the chest wall and supraclavicular region in 5 of 8 patients, chest wall only in 1 of 8 patients and chest wall, supraclavicular region, and internal mammary region in 2 of 8 patients. Adjuvant or neoadjuvant chemotherapy were administered to 8 of 8 patients.

Clinical courses

The clinical courses of group A patients are summarized in Table 3. The time periods between the completion of radiotherapy and ISR were ranged from 1 to 27 months (median, 3.5 months). Pathological confirmation of the inflammatory recurrent site was performed in 6 of 8 patients. ISR was the initial solitary site of recurrence after postoperative radiotherapy in 3 of 8 patients. Two patients developed inflammatory local recurrence and regional lymph-nodes or lung metastases simultaneously. Three other patients had preceding distant metastases. All 8 patients in group A subsequently developed distant metastases and died of disease in 3–16 months.

The group B patient clinical courses are summarized in Table 4. The time periods between the completion of radiotherapy and the occurrence of ISR ranged from 2 to 33

Table 1. Characteristics of the patients after breast conserving therapy (BCT) (Group A)

Pt. No.	Age	Histology	pT*	pN*	p-stage	ly	v	Margin	ER/PR	Her2	RT(Gy)	Adjuvant Cx	Adjuvant Ex
1	86	IDC	1a	2a	IIIA	+++	+	–	–/–	?	50,br.sc	–	–
2	42	IDC	2	1	IIB	+	+	–	–/+	?	48,br	+	+
3	61	IDC	1c	1	IIA	–	–	+	–/–	+	60,br	+	–
4	60	IDC	2	2a	IIIA	?	?	–	+/–	–	50,br.sc	+	?
5	62	DCIS	is	0	0	–	–	+	–/–	+	60,br	–	?
6	54	IDC	1c	3a	IIIC	+++	–	+–	–/–	+	50,br.sc	+ (neoadjuvant)	–
7	64	IDC	1b	2a	IIIA	–	?	–	–/–	–	50,br	+	–
8	63	IDC	1c	1	IIA	+++	–	–	–/–	–	50,br	+	–

*: UICC 6th ed.

Abbreviations: IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, ly = lymphatic invasion, v = vascular invasion, br = breast, sc = supraclavicular, Cx = chemotherapy, Ex = endocrine therapy, +– = close margin.

Table 2. Characteristics of the patients following post mastectomy radiotherapy (PMRT) (Group B)

Pt. No.	Age	Histology	pT*	pN*	p-stage	ly	v	Margin	ER/PR	Her2	RT(Gy)	Adjuvant Cx	Adjuvant Ex
9	67	IDC	1c	3a	IIIC	++	+	–	–/–	+	50,cw.sc	+	+
10	52	IDC	3	2	IIIA	–	–	–	–/+	–	50,cw.sc	+	+
11	48	IDC	3	2a	IIIA	++	–	–	–/–	+++	50, cw.sc.im	+	+
12	65	IDC	4b	1	IIIB	++	+	+	?/?	?	50,cw.sc	+ (neoadjuvant)	?
13	61	IDC	2	1	IIB	++	+	–	–/–	+	50,cw.sc	+	+
14	49	IDC	3	1	IIIA	+	–	–	–/–	–	51,cw	+	+
15	60	IDC	2	3a	IIIC	+	+	–	–/–	+	50, cw.sc.im	+ (neoadjuvant + adjuvant)	–
16	38	IDC	2	2a	IIIA	+	–	–	+ /+	++	50,cw.sc	+	+

*: UICC 6th ed.

Abbreviations: IDC = invasive ductal carcinoma, ly = lymphatic invasion, v = vascular invasion, br = breast, sc = supraclavicular, cw = chest wall, sc = supracalvicular, im = internal mammary, Cx = chemotherapy, Ex = endocrine therapy.

Table 3. Clinical course of the patients after BCT (Group A)

Pt. No.	Skin rec site	Surgery-ISR interval	RT-ISR interval	Rec site before ISR	Therapy after ISR	Rec site after ISR	Outcome
1	br	9 M	1.5 M	–	Cx + RT	Pleura, distant LN	14 M DOD
2	br	11 M	8 M	–	Cx + Ex + hyperthermia	Regional LN (simultaneous), pleura	3 M DOD
3	br	29 M	27 M	Lung	Cx	Brain, liver, distant LN	7 M DOD
4	sc	49 M	1 M	Pectoral muscle	Cx	pleura	13 M DOD
5	br	6 M	4 M	–	Cx	Lung (simultaneous), brain, distant LN	16 M DOD
6	br+sc	6 M	3 M	–	Cx	Lung, distant LN, pleura	8 M DOD
7	br	14 M	3 M	Pleura	Cx	Distant LN	6 M DOD
8	br	14 M	4 M	–	Cx + surgery	Chest wall	11 M DOD

Abbreviations: ISR = inflammatory skin recurrence, rec = recurrence, Cx = chemotherapy, Ex = endocrine therapy, RT = radiotherapy, HT = hyperthermia, LN = lymphnode, DOD = died of disease, AWD = alive with disease.

months (median, 8.5 months). Pathological confirmation of the inflammatory recurrent site was performed in 7 of 8 patients. ISR was the initial solitary site of recurrence after postoperative radiotherapy in 5 of 8 patients. Two patients developed inflammatory local recurrence and distant metastases simultaneously. The remaining 1 patient had preceding distant metastases (supraclavicular lymph node recurrence in the opposite side). All 8 patients in group B subsequently developed distant metastases. Four patients died of disease in 16–36 months, 3 patients lived with disease in 14–39 months and 1 patient survived with no evidence of disease for 67 months after the inflammatory recurrence. The overall survival curves are shown in Fig. 1.

Median survival periods were 8.9 months in group A and 36.8 months in group B (p = 0.0001).

Estimation of the incidence of ISR

Ten out of 11 institutes completed the third survey. The total number of patients treated with postoperative radiotherapy for breast cancer at these 10 institutes between 1992 and 2005 (initial year was different in each institute, ranging from 1992 to 2001) was 6061. From these 10 institutes, 15 patients were enrolled in this study. Thus, estimation of the incidence of ISR affecting the previous radiation fields after BCT or PMRT was considered to be approximately 0.25% (15/6061).

Table 4. Clinical course of the patients after PMRT (Group B)

Pt. No.	Skin rec site	Surgery-ISR interval	RT-ISR interval	Rec site before ISR	Therapy after ISR	Rec site after ISR	Outcome
9	cw, sc, ax	21 M	19 M	–	Cx	Contralateral breast (simultaneous), pleura	25 M DOD
10	cw	23 M	21 M	–	RT + Cx	Contralateral breast, cervical LN	67 M NED
11	cw, im	13 M	11 M	–	Cx	Ax, parotid LN, contralateral Ax	36 M DOD
12	cw	4 M	2 M	–	Cx	Pleura, pericardium	16 M DOD
13	cw	37 M	33 M	–	Cx	Distant LN	14 M AWD
14	cw	13 M	3 M	–	Cx + Ex + RT	SCLN, lung, bone, pleura, brain	25 M DOD
15	cw, im	8 M	2 M	+	Cx	Contralateral Ax	39 M AWD
16	cw	15 M	6 M	Contralateral SCLN	Cx + RT	Distant skin, meninges, bone	22 M AWD

Abbreviations: ISR = inflammatory skin recurrence, rec = recurrence, Cx = chemotherapy, Ex = endocrine therapy, RT = radiotherapy, HT = hyperthermia, LN = lymph node, DOD = died of disease, AWD = alive with disease, NED = no evidence of disease.
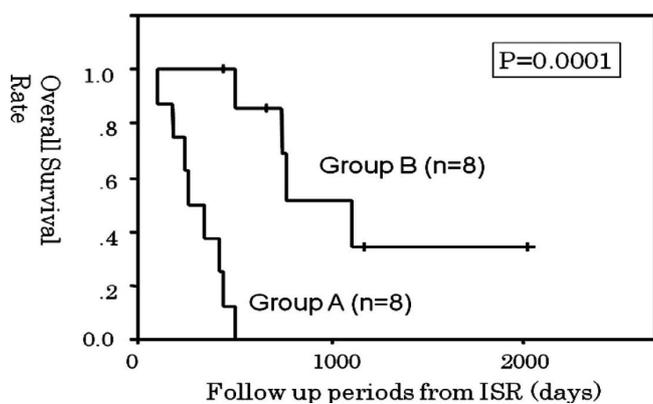
**Fig. 1.** Overall survival curve by the group.

Fig. 2. Case6: 3 months after radiotherapy to right breast and supraclavicular region.

Case presentation

Case No.6: A 54-year–old postmenopausal woman who was diagnosed with cT2N1M0 right breast cancer and underwent neoadjuvant chemotherapy consisting of 4 courses of cyclophosphamide, epirubicin, fluorouracil and 4 courses of docetaxel followed by quadrantectomy and axillary dissection. Postoperative pathology showed an invasive ductal carcinoma (16 mm) of nuclear grade 3, a massive lymphatic invasion, and a close surgical margin. ER and PR status were negative and Her2 status was positive. Axillary lymph-nodes were positive for 23 out of 31 nodes. Postoperative radiotherapy of 50 Gy/25 fr by ^{60}Co was delivered to the right breast and right supraclavicular region. Three months after the completion of radiotherapy, ISR sharply matched to the area of previous irradiation fields was observed (Fig. 2). Skin biopsy revealed the same histology

as the primary breast cancer in the dermal collagen tissue. Salvage chemo-endocrine therapy was administered including trastuzumab and capecitabine. However, multiple lung metastases and mediastinal lymph-node metastases developed 6 months after the completion of radiotherapy. The patient died of disease 1 year after radiotherapy without responding to the additional chemotherapy, including paclitaxel and vinorelbine.

Case No.9: A 67-year-old postmenopausal woman diagnosed with cT1cN0M0 invasive ductal carcinoma of the left breast. She underwent a modified RM. Pathology revealed
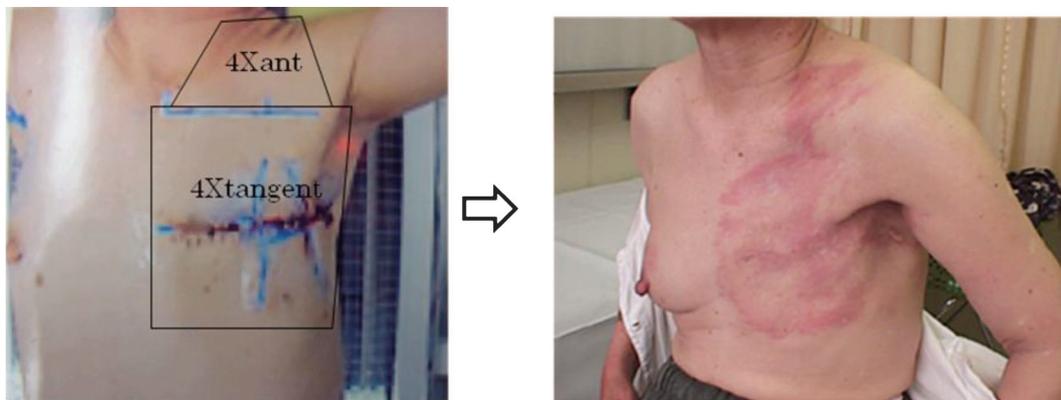
Fig. 3. Case9: radiation fields and 21 months after completion of radiotherapy.

an invasive ductal carcinoma (15 mm) with prominent lymphatic invasion and intraductal invasion. Axillary lymph-nodes were positive for metastases in 39 of 40 nodes. ER and PR status were negative and Her2 status was positive. The pathological stage was pT1cN3aM0, stage IIIC. PMRT of 50 Gy/25 fr was delivered to her left chest wall and supraclavicular region with a 4 MV photon beam. Adjuvant chemo-endocrine therapy was administered with oral doxifluridine and MPA concurrently with PMRT until the ISR was observed. Seven months later after the completion of PMRT, the patient suddenly developed an erythematous rash over her left chest wall and left supraclavicular region sharply matched to the previous PMRT area (Fig. 3). At the same time, a small area of erythema appeared on her right breast skin. Cytology of the right breast skin revealed tumor cells in the dermis and lymphatic invasion compatible with recurrent breast cancer. Salvage chemotherapy was given with paclitaxel, epirubicin, and trastuzumab, and skin erythema had almost diminished 3 months later. However, bilateral malignant pleural effusion appeared subsequently and the patient died of disease 46 months after mastectomy.

DISCUSSION

The current survey is the first report of multi-institutional experience with ISR. It revealed that ISR after PMRT or BCT is not a common event but approximately 1 of 4 radiation oncologists have some experiences with ISR in the area corresponding to a previous field of postoperative radiotherapy and the estimated incidence was approximately 0.25% of breast cancer patients who had postoperative radiotherapy. ISR exactly demarcating the previously irradiated normal skin area is a rare event but several case reports have been published since 1960'. Most cases were breast cancer patients after PMRT[5,6] and some cases were other patients including those with nasopharyngeal cancer, endometrial cancer, and cervical cancer.[7–9] In the breast cancer cases, there is some concern that residual cancer cells

are present before radiotherapy. However, the sharp straight line of the ISR area, which matched the radiation field, suggests that radiotherapy was the predominant factor for the occurrence of ISR. ISR corresponding to the previously irradiated area is sometimes difficult to distinguish from acute or chronic radiation dermatitis.[10,11]

The incidences of the inflammatory type of inoperable ipsilateral breast recurrence was reported to be 0.4–6.8% of the cases treated with BCT, and represented 12–32% of all ipsilateral breast recurrences.[12–16] The prognoses after inflammatory recurrence were very poor and the mean survival period reported was less than 2 years.[14] Some of these earlier cases may have been ISR confined to the area of previous irradiation, however, we could not find any reports that mentioned whether the recurrence matched the irradiated area. Patients after breast conserving surgery without radiotherapy also developed inflammatory recurrence in some reports.[15,16] However, Nishimura et al. also reported that inflammatory recurrences were more common in those who received radiotherapy (inflammatory: non- inflammatory = 6:3) whereas in those who had not received radiotherapy, non-inflammatory recurrence was more common (18:46).[15] Nishimura et al. suggested that radiation caused lymphatic retention, leading to the formation of tumor emboli in the area where lymphatic fluid was retained. The positive surgical margin and nonradiation therapy which have been shown to be significant risk factors for noninflammatory breast recurrence were entirely unrelated to inflammatory breast recurrence. They reported risk factors related to inflammatory recurrence as positive axillary lymph-nodes metastasis and positive lymphatic invasion. Another study showed the time to inflammatory recurrence was considerably shorter in ER-negative patients compared with ER-positive patients.[16] The current survey also showed high rates of positive axillary lymph-nodes metastases, positive lymphatic invasion, and negative ER status.

In patients after PMRT, inflammatory-type skin recurrence was reported as an impairment to overall survival com-

pared to ordinary-type skin recurrence.[17] In the current survey, prognosis of PMRT patients was better than that of BCT patients. One reason for this may be that skin recurrences were the initial solitary site of recurrence in 5 of 8 patients.[18]

The mechanism of ISR confined to the area of previous irradiation has not been clearly understood. Experimental studies in the 1970s and 1980s showed an interesting phenomenon similar to this type of recurrence. Tumor cells injected into experimental animals previously treated with local thoracic irradiation (LTI) generated several times more metastatic nodules in the lungs than when injected into untreated animals.[19–21] An extensive review of this phenomenon was published by Milas and Peters.[22] They suggested that the enhancement of lung nodule formation in the lung of treated mice could result from local microenvironment changes caused by LTI rather than systemic immunosuppressive effects. Radiation can cause subtle changes in the capillary walls, making it easier for tumor cells to pass into the perivascular connective tissue.[23,24] The clinical significance of breast cancer recurrence throughout a chest wall that received radiotherapy may be that this results from an effect of lymphatics similar to that described above for lung capillaries.[19] The blockage of the deep dermal lymphatics and lymph-nodes by irradiation may induce cancerous embolus of the dermal lymphatic vessel.

Recent experimental studies revealed that thoracic irradiation caused increased circulating levels of TGF-beta1, as well as lung metastases in the irradiated lung. These effects were blocked by the administration of TGF-beta-neutralizing antibody. These data suggested the increase of lung metastases was at least in part due to a direct effect of TGF-beta on the cancer cells.[25] Another experimental study showed that a sublethal dose of radiation enhances the invasiveness of HCC cells, mainly through matrix metalloproteinase-9 expression mediated by the PI3K/Akt/ NF-kB signal transduction pathway.[26]

Some authors speculated that a subcurative dose of radiation promoted the invasiveness of the cancer cells and facilitated the local spread of tumor growth within the irradiated skin.[27] On the other hand, an experimental study showed a dose-response relationship for enhancement of lung colony-forming efficiency by irradiation.[28] In the current survey, ISR had occurred even though patients were treated with 48–50 Gy for the postoperative setting of breast cancer. Fifty Gy is considered to be sufficient for preventing local recurrence in the postoperative state of standard breast cancer, but dermal/sub-dermal dose might be lower than 50 Gy in some cases. However, even if dermal/sub-dermal dose was 50 Gy using bolus or electron beam, it may be insufficient for more aggressive cancer such as multiple lymph-node metastases or intensive lymphatic invasion.

In conclusion, patients who developed ISR tended to have several characteristics including positive lymph-node metastases, intensive lymphatic invasion, and a negative ER status. All cases developed distant metastases subsequently and prognoses were dismal. However, in some patients after PMRT, longer survival was sometimes obtained with salvage therapy. In cases of unusual skin change corresponding to the previously irradiated area after post operative radiotherapy, physicians should also contemplate the diagnosis of ISR next to radiation recall or radiation dermatitis, especially when the aforementioned risk factors are present.

REFERENCES

1. Touboul E, *et al* (1999) Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. Int J Radiat Oncol Biol Phys **43**: 25–38.
2. Buchanan CL, *et al* (2006) Locoregional recurrence after mastectomy: incidence and outcomes. J Am Coll Surg **203**: 469–474.
3. Huang EH, *et al* (2005) Predictors of locoregional recurrence in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiotherapy. Int J Radiat Oncol Biol Phys **62**: 351–357.
4. Lever LR and Holt PJ (1991) Carcinoma erysipeloides. Br J Dermatol **124**: 279–282.
5. Dao T and Kovaric J (1962) Incidence of pulmononary and skin metastases in woman with breast cancer who received postoperative irradiaion. Surgery **52**: 203–212.
6. Cole H and Halnan KE (1971) Facilitation of tumour spread in irradiated tissue after prophylactic post-operative x-ray therapy for breast cancer. Clin Radiol **22**: 133–135.
7. Meltzer J, Ahmed SA and Archambeau JO (1981) The development of metastases within a field of previous irradiation: a case report. Cancer **48**: 717–720.
8. Marley NF and Marley WM (1982) Skin metastases in an area of radiation dermatitis. Arch Dermatol **118**: 129–131.
9. Luh JY, *et al* (2004) Skin metastasis in a previously irradiated field from squamous cell carcinoma of the cervix. Southern Medical Journal **97**: S29.
10. Takashima S, *et al* (1996) Analysis of local recurrences after breast conserving therapy using postoperative radiotherapy. Gan To Kagaku Ryoho **23**(Suppl 1): 84–91.
11. Pakula AS and Robinson JK (1992) Recognizing malignant skin changes following breast cancer. Am Fam Physician **45**: 1287–1292.
12. Fisher ER, *et al* (1986) Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. Cancer **57**: 1717–1724.
13. Sibbering DM, *et al* (1995) Safe selection criteria for breast conservation without radical excision in primary operable invasive breast cancer. Eur J Cancer **31A**: 2191–2195.
14. Kurtz JM, *et al* (1991) Inoperable recurrence after breast-conserving surgical treatment and radiotherapy. Surg Gynecol Obstet **172**: 357–361.
15. Nishimura R, *et al* (1998) A case control study on risk factors involved in inflammatory breast recurrence after breast-conserving surgery. Oncology **55**: 391–399.

16. Huston TL and Simmons RM (2005) Inflammatory local recurrence after breast-conservation therapy for noninflammatory breast cancer. Am J Clin Oncol **28**: 431–432.

17. Jaffre F, *et al* (2009) Prognosis for isolated skin recurrence after breast cancer treated by mastectomy. Anticancer Res **29**: 1697–1701.

18. Willner J, Kiricuta IC and Kolbl O (1997) Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. Int J Radiat Oncol Biol Phys **37**: 853–863.

19. Withers HR and Milas L (1973) Influence of preirradiation of lung on development of artificial pulmonary metastases of fibrosarcoma in mice. Cancer Res **33**: 1931–1936.

20. Brown JM (1973) The effect of lung irradiation on the incidence of pulmonary metastases in mice. Br J Radiol **46**: 613–618.

21. Lacina NC, *et al* (1978) Topical clindamycin for acne. Part 1: current prescribing practices. Am Pharm **18**: 30–33.

22. Milas L and Peters LJ (1984) Conditioning of tissues for metastasis formation by radiation and cytotoxic drugs. In: GL N and Milas L eds. *Cancer invasion and metastasis: biologic and therapeutic aspects*. pp. 321–335. Raven Press, New York.

23. Peters LJ, *et al* (1978) Enhancement of lung colony-forming efficiency by local thoracic irradiation: interpretation of labeled cell studies. Radiology **126**: 499–505.

24. Hirata H and Tanaka K (1984) Artificial metastases and decrease of fibrinolysis in the nude mouse lung after hemithoracic irradiation. Clin Exp Metastasis **2**: 311–319.

25. Biswas S, *et al* (2007) Inhibition of TGF-beta with neutralizing antibodies prevents radiation-induced acceleration of metastatic cancer progression. J Clin Invest **117**: 1305–1313.

26. Cheng JC, *et al* (2006) Radiation-enhanced hepatocellular carcinoma cell invasion with MMP-9 expression through PI3K/Akt/NF-kappaB signal transduction pathway. Oncogene **25**: 7009–7018.

27. von Essen CF (1991) Radiation enhancement of metastasis: a review. Clin Exp Metastasis **9**: 77–104.

28. Peters LJ and Mason K (1980) Effect of lung irradiation on metastases: Radiobiological studies amd clinical correlations. In: Meyn RE and Withers HR eds. *Radiation biology in Cancer Research*. pp. 515–529. Raven Press, New York.