Original Study

Modified Simultaneous Integrated Boost Radiotherapy for Unresectable Locally Advanced Breast Cancer: Preliminary Results of a Prospective Clinical Trial☆

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Abstract

Unresectable massive T4 breast tumor cannot be controlled by radiotherapy of ≤70Gy. Modified SIB irradiation technique enables to irradiate ≥100Gy to the tumor, keeping dose to the surrounding healthy tissue within tolerance dose. Huge tumors of all 3 patients enrolled in the clinical trial macroscopically disappeared by modified SIB radiotherapy.

Background: The purpose of this study was to evaluate the effect of modified simultaneous integrated boost (SIB) radiotherapy for patients with extensive breast cancer. **Patients and Methods:** Patients with macroscopic tumor and histologically proven adenocarcinoma of the breast were enrolled in the study. Patients were included whether they had or did not have previous surgery, chemotherapy, hormone therapy, or molecular targeted therapy; patients with past history of thoracic radiotherapy were excluded. Under conditions of not exceeding the tolerance dose for normal tissue, irradiation to the tumor was increased to the maximum possible extent using the modified SIB technique. **Results:** Three breast cancer patients were treated with the modified SIB technique. All patients were diagnosed as T4b (median maximum diameter of the tumor: 16 cm; range, 15.5-22 cm), and all patients exhibited symptoms because of the extremely large tumor. The median total dose to the part of tumor tissue was 128.8 Gy (range, 110-140 Gy). Total dose to normal tissue was < 72 Gy in all patients. Although large tumors were radioresistant, it was macroscopically confirmed that all tumors eventually disappeared. Although skin defects persisted because of tumor disappearance, there were no Grade ≥ 3 toxicities due to radiotherapy. **Conclusion:** Although much care is required in delivering extremely high doses of radiotherapy to the tumor, modified SIB radiotherapy was shown to be effective against extremely large tumors that could not be controlled using conventional radiotherapy. In future, an increase in the number of study patients and establishment of the technique will be required.

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Introduction

The incidence of advanced breast cancer is 80-120 per 1,000,000 people.[1,2] For patients with locally advanced breast cancer, chemotherapy, radiotherapy (RT), and hormone therapy are mainly performed when the tumor is deemed unresectable.[3,4] The primary drugs used for induction chemotherapy are as follows: anthracycline

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(doxorubicin), taxanes (paclitaxel and docetaxel), cyclophosphamide, 5-fluorouracil, and so on.

In some cases, curative surgery and postoperative RT are performed for good responders to induction chemotherapy; in other cases, chemotherapy (and/or RT) is performed for nonresponders to induction chemotherapy.[2] However, a standard treatment for locally advanced breast cancer (eg, large T4 tumor) has yet to be established. In this study, we used a new irradiation technique for advanced breast cancer patients, and report the efficacy and feasibility of this new approach.

Patients and Methods

Patients

Our investigation was designed as a prospective study of modified simultaneous integrated boost (SIB) RT for far-advanced cancer. The primary end point was defined as local response (rate of complete response and partial response); secondary end points were defined as toxicity, quality of life (QOL), and overall survival rate. Histologically proven breast cancer patients with large ($\geq$ 10 cm) and unresectable tumors were enrolled in the study. Patients were enrolled in the study regardless of the presence or absence of previous surgery, chemotherapy, and/or hormone therapy. Patients with untreated advanced breast cancer, recurrent breast cancer, and treatment-resistant breast cancer were also included in the study. However, patients with a past history of thoracic RT were excluded. Patients aged 20 years or older were included, as were patients with a performance status of 0 to 4. Written informed consent was obtained from all enrolled patients. This study was been approved by the institutional review board (H22-97).

Radiotherapy

Four- to 10-MV photon and 4- to 20-megaelectron volt (MeV) electron beams from a high-energy linear accelerator were used for treatment. Irradiation was performed once a day with 5 fractions per week. Immobilization devices were used as necessary. Skin markers and image guidance (using flat panel detector) were used in the setup process. Irradiation was performed under shallow breathing without respiratory gating. Computed tomography-based RT planning was performed using XiO (Elekta Inc, Tokyo, Japan), and dose distribution was calculated using a superposition algorithm. The macroscopic tumor was defined as gross target/tumor volume (GTV), and metastatic lesion was also regarded as GTV. The subclinical region (10 mm) around GTV and level I to III axillary lymph node (LN) area (and supraclavicular LN area if there was LN metastasis) was defined as clinical target volume (CTV). The target volume, including CTV and setup margins of 5 to 10 mm, was defined as planning target volume (PTV).

Modified SIB Technique

The standard SIB technique involves irradiating CTV with a prophylactic dose and GTV with a curative dose. For example, RT with standard SIB is used for head and neck tumors with regional LN metastasis. The technique enables a prophylactic dose of radiation to be delivered to the LN region with higher doses to the primary tumor and metastatic lesion.[5-7] Because a complex dose

Table 1 Patient Characteristics

Patient	Age, Years	Sex	TNM	Stage	Primary Lesion	Histology	History of Chemotherapy	Tumor Diameter (Maximum)	Metastasis	Symptoms
1	62	F	T4bN2M0	IIIb	Right breast	IDC (solid-tubular)	Weekly PTX x4 (courses), FEC x5, 3 Weekly DOC x3 (PD)	15.5 cm	AxLN	Skin ulcer, pain, bleeding
2	48	F	T4bN3M1	IV	Left breast	IDC (solid-tubular)	FEC x3, DOC x3, TS-1 daily (PD)	16 cm	AxLN, lung, liver	Skin ulcer, pain, edema
3	58	F	T4bN1M1	IV	Left breast	IDC (scirrhous)	FEC x2, Weekly PTX with HER x4, VNB with HER x1 (PD)	22 cm	ScLN	Skin ulcer, pain, edema, bleeding

Abbreviations: AxLN = ipsilateral axillary lymph node(s); DOC = docetaxel; F = female; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; HER = Herceptin (trastuzumab); IDC = invasive ductal carcinoma; PTX = paclitaxel; ScLN = supraclavicular lymph node(s); TNM = tumor, node, metastases; TS-1 = tegafur-gimeracil-oteracil potassium; VNB = vinorelbine.