Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Mapping patterns of locoregional recurrence following contemporary treatment with radiation therapy for breast cancer: A multi-institutional validation study of the ESTRO consensus guideline on clinical target volume

Jee Suk Chang [a,1], Jeongshim Lee [b,1], Mison Chun [c], Kyung Hwan Shin [d], Won Park [e], Jong Hoon Lee [f], Jin Hee Kim [g], Won Sup Yoon [h], Ik Jae Lee [i], Juree Kim [j], Hye Li Park [k], Yong Bae Kim [a,*]

[a] Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul; [b] Department of Radiation Oncology, Inha University Hospital, Incheon; [c] Department of Radiation Oncology, Ajou University School of Medicine, Suwon; [d] Department of Radiation Oncology, Seoul National University College of Medicine; [e] Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [f] Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon; [g] Department of Radiation Oncology, Dongsan Medical Center, Keimyung University School of Medicine, Daegu; [h] Department of Radiation Oncology, Ansan Hospital, Korea University Medical Center, Ansan; [i] Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul; [j] Department of Radiation Oncology, Cheil General Hospital, Dankook University College of Medicine, Seoul; and [k] Department of Radiation Oncology, Presbyterian Medical Center, Jeonju, Republic of Korea

ARTICLE INFO

Article history:
Received 18 July 2017
Received in revised form 13 September 2017
Accepted 23 September 2017
Available online xxxx

Keywords:
Breast cancer recurrence
Clinical target volume
Recurrence patterns
Radiation therapy

ABSTRACT

Background and purpose: To validate the ESTRO guideline on clinical target volume (CTV) delineation for breast cancer using a multi-centre dataset.

Materials and methods: Patients with axial imaging of gross locoregional recurrence (LRR) were identified from 10 participating institutions. All patients received RT, albeit not to all regional node. The location of LRR was transferred to the corresponding area on representative axial computed tomography images and compared with ESTRO-CTV.

Results: The locations of LRRs in 234 patients with 337 recurrence lesions were mapped. The ESTRO-CTV encompassed 97.6% of all LRRs, except in lymph node level 4 and the pectoralis muscle. Although 8.8% of level 4 failures occurred outside the ESTRO-CTV, cranial to the subclavian artery, all nodes were located within 6 mm cranially. Another 20% occurred posterolateral to anterior scalene muscles; however, 11/16 cases had simultaneous multiple lymph node recurrences, and 8/16 initially had N2-3 tumours. Local recurrence at the pectoralis muscle was prominent in patients undergoing mastectomy but not breast-conservation surgery (28% vs. 2.9%, $P = .001$).

Conclusions: Our mapping data demonstrated that the ESTRO-CTV, with some considerations, successfully encompassed most LRRs in patients undergoing contemporary management, thus validating ESTRO-CTV to be valuable for highly conformal radiation therapy techniques.

After thyroid cancer, breast cancer is the second most common cancer among women in Korea, with an incidence of 72.1 per 100,000 population in 2014 [1]. In Korea, unlike other cancers, the breast cancer incidence is showing an increasing trend and this trend is expected to continue as the life expectancy of Korean women surges at the highest pace in the world [2,3]. Although radiation therapy (RT) is an essential local therapy for both mastectomy and breast-conserved patients to improve local control and survival, acute and late toxicities might lead to reduced cosmesis and quality of life [4,5].

Intensity-modulated radiation therapy (IMRT) enables the delivery of irradiation with improved dose distribution while minimizing the dose to the organs at risk [6]. Many studies have demonstrated that IMRT can reduce RT-related acute toxicity and chronic breast oedema when compared with conventional techniques [7,8]. Because the National Health Insurance Service have reimbursed IMRT since 2015 in Korea, increasing number of breast cancer patients now undergo this treatment, and the usage of IMRT has increased compared to three-dimensional conformal therapy. Currently, the proposed guidelines from the Radiation Therapy Oncology Group (RTOG) and European Society for Therapeutic

* Corresponding author at: Yonsei Cancer Center, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. Fax: +82 2 2227 7823.
E-mail address: ybkim3@yuhs.ac (Y.B. Kim).
[1] J.S.C. and J.L. contributed equally to this work.

https://doi.org/10.1016/j.radonc.2017.09.031
0167-8140/

Radiology and Oncology (ESTRO) are the most widely used [9–11]. Of the two, the ESTRO-clinical target volume (CTV) guideline, which was created specifically for the purpose of treating early-stage breast cancer, has been getting more attention lately, owing to increasing number of patients with early-stage disease at diagnosis.

We previously demonstrated the three-dimensional mapping of locoregional recurrence (LRR) patterns to validate the ESTRO-CTV in patients with early-stage tumours in relation to the RTOG-CTV [12]. However, our previous study had some limitations, including its single institutional study design, the inclusion of patients before the era of anti-HER2 targeted therapy, and the inclusion of patients regardless of their previous history of RT for breast cancer. Thus, on the basis of our previous data, we designed the present multi-institutional validation study with the aim to further validate and generalize our findings in a more contemporary cohort of patients treated with breast or chest wall irradiation after 2006. The second aim of this study was to identify the risk factors for geographic target misses that should be taken into consideration for target volume delineation using the ESTRO-CTV.

Materials and methods

Study design

In July 2015, the Korean Radiation Oncology Group (KROG 15-07) initiated a multi-institutional retrospective mapping study to explore the validity of the ESTRO-CTV for breast cancer patients treated with more contemporary treatment [13]. The target study population was defined as patients who had LRR with or without simultaneous distant metastasis as the first event and who had undergone breast surgery with adjuvant RT between 2006 and 2014. Computed tomography (CT) with or without positron emission tomography (PET) images, previous RT field information, and available medical charts were mandatory for participation in the study. We excluded patients with initial stage IV or clinical N3 stage disease and a history of other malignancy except for thyroid malignancy and early gastric cancer, which are common but curable in Korea. All image files were collected on the online study website in the format of Digital Imaging and Communications in Medicine (DICOM). All data were conveyed after encryption and anonymization. The images were reviewed centrally by two independent and blinded investigators (JL and JSC) who had previous experience with this type of analysis. Finally, a total of 234 patients from 10 institutions who met the eligibility criteria were included in this study. This retrospective study was approved by the review board of the KROG and by the Institutional Review Boards of all participating institutions. The informed consent was waived due to retrospective nature.

Radiation therapy

For patients undergoing breast conservation surgery, the whole breast was irradiated with a median dose of 50.4 Gy (range, 45–50.4 Gy) in 28 fractions. Tumour bed boost RT was delivered in 186 patients (79.5%), with a median dose of 9.0 Gy (range, 8.0–15 Gy) in 5 fractions. For post-mastectomy patients, the chest wall was irradiated with a median dose of 50.4 Gy (range, 50–64.4 Gy) in 28 fractions. Chest wall RT was administered to all patients. Regional RT was used in 6.3%, 48.1%, and 98% of patients with N0, N1, and N2-3 disease, respectively.

Mapping and analysis

The mapping and analysis methods used were similar to those used in our previous study [12]. Briefly, one patient (156 cm, 54 kg, body mass index 22.27 kg/m^2) subjected to breast conservation surgery and one patient (160 cm, 57 kg, body mass index 22.19 kg/m^2) subjected to mastectomy were selected as standard representative patients. Next, we first contoured the axillary vein, subclavian vein, jugular vein, and internal mammary vein on the reference CT images. Finally, we mapped all LRRs manually at the equivalent location on the reference images in relation to the veins. To reduce volume effects, we transformed each tumour to a 5-mm spot at the epicentre.

The RTOG-CTV [11] and ESTRO-CTV [9,10] were delineated by experienced investigators, blinded to the location of LRR, according to the guidelines. LRRs were classified into three categories: (1) inside ESTRO vs. (2) outside ESTRO, inside RTOG vs. (3) outside RTOG. Maximum-intensity projection images were reconstructed from two-dimensional axial contours using MIM software (version 6.46, MIM Software Inc., Cleveland, OH, USA).

Either the Chi-square or Fisher's exact test was used to compare the patterns of local and regional recurrence. All statistical analyses were conducted using R software (www.r-project.org).

Results

Patient characteristics

Table 1 shows the clinical characteristics of the study patients. The median disease-free interval for our cohort was 1.9 years

Table 1
Patient characteristics.

	Pt No.	%
Age, years	47 (median)	19–75 (range)
≤45	107	46%
>45	127	54%
Tumour laterality		
Right breast	113	48%
Left breast	121	52%
Tumour location		
Inner	55	24%
Central/Outer	179	77%
Final T stage[†]		
T0	1	0%
T1	72	31%
T2	127	54%
T3	25	11%
T4	9	4%
Final N stage[†]		
N0	79	34%
N1	54	23%

Please cite this article in press as: Chang JS et al. Mapping patterns of locoregional recurrence following contemporary treatment with radiation therapy for breast cancer: A multi-institutional validation study of the ESTRO consensus guideline on clinical target volume. Radiother Oncol (2017), https://doi.org/10.1016/j.radonc.2017.09.031