Phase II study on the use of intraoperative radiotherapy in early breast cancer

Adnan A. Merdad, MBBS, FRCSC, *Yasir A. Bahadur,* MD, FRCPC, *Ehab E. Fawzy,* MD, PhD, *Ashraf H. Hassouna,* MD, PhD, *Maha M. Eltaher,* MD, PhD, *Zuhoor K. Alghaithy,* MD, FRCSI, *Fatma K. Al-Thoubaity,* MBBS, FRCSI, *Camelia T. Constantinescu,* MSc, PhD.

ABSTRACT

الأهداف: توثيق التجارب الأولية لاستخدام طريقة المعالجة بالإشعاع عن طريق الإشعاع الداخلي للمعالجة الإشعاعية خلال العملية الجراحية وذلك في المراحل المبكرة من سرطان الثدي.

الطريقة: أجريت هذه الدراسة المستقبلية من المرحلة 2 في قسم الجراحة والمعالجة الإشعاعية، مستشفى الملك عبدالعزيز، جدة، المملكة العربية السعودية خلال الفترة من ديسمبر 2010م إلى نوفمبر 2012م. اشتملت الدراسة على نساء مؤهلات لجراحة الحفاظ على الثدي مصابين بسرطان اجتياحي في القنوات مثبت عن طريق الخزعة مكون من كتلة ≤ 3.5سم. بعد قطع موضعي عريض وتشريح عقدة لمفاوية أساسية ووضع الأداة الطبية ذات عيار مناسب بطريقة جراحية على قاع الورم. تم وصف جرعة واحدة من 20 جراي باستخدام مولد الأشعة السينية ذات الإشعاع الداخلي. المعالجة بالإشعاع عن طريق الإشعاع الخارجي (46 EBRT؛ جراي/ 23 مقسم على 4.5 أسابيع تم إعطاءه عندما كان الورم أقل من 3 سم مع اجتياح لمفاوي وريدي وضرر متعدد في البؤر وسرطان متفشي في القنوات وورم مؤكد. تم رصد تسمم مبكر ومتأخر باستخدام مقياس مجموعة علاج الأورام بالإشعاع (RTOG).

النتائج: اشتملت الدراسة على 45 مريض، متوسط العمر 54 عام المدى (27–79) عام. 36 حالة كان لديهم ورم أكثر من 3 سم في القطر، و36 (76%) لديهم نمو عقدة لمفية إبطيه سالبة. لم يظهر أي تأخر في التام اجرح أو التهاب بعد الجراحة تتطلب مضاد حيوي وريدي أو تورم مصلي في الثدي يتطلب تفريغ. تلقى 16 (36%) الإشعاع الخارجي بعد IORT وظهر تنكرز دهني مثبت شعاعياً عند 12 مريض.

خاتمة: استخدام IORT لمرضى سرطان الثدي ذو المرحلة المبكرة عن طريق نظام توصيل الإشعاع الداخلي تم تنفيذه بسهولة في مركزنا بنسبة تسمم ونتيجة تجميلية مقبولتان.

Objectives: To report our early experience using the Intrabeam radiotherapy delivery system for intraoperative radiotherapy (IORT) in early breast cancer.

Methods: This is a prospective phase 2 study carried out at the Department of Surgery and Radiology, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia from December 2010 to November 2012. Females eligible for breast-conserving surgery with biopsy-proven invasive duct carcinoma, and with a mass of ≤3.5 cm were included in this study. After wide local excision, sentinel lymph node dissection, and surgically positioning of the appropriately sized applicator on the tumor bed, a 20 Gray (Gy) single dose was prescribed using the Intrabeam x-ray generator. External beam radiotherapy (EBRT; 46 Gy/23 fractions/4.5 weeks) was given when the tumor was >3 cm, with lymphovascular invasion, multifocal lesion, extensive intraductal carcinoma, and positive nodes. Early and late toxicity were recorded using the Radiation Therapy Oncology Group (RTOG) criteria.

Results: Forty-five patients were included with a median age of 54 (range: 27-79 years). Thirty-six cases (80%) had tumor <3 cm in diameter, and 36 (67%) have pathologically negative axillary lymph node metastases. None of the patients developed delayed wound healing, postoperative infection requiring intravenous antibiotic, or breast seroma requiring aspiration. Sixteen (36%) received EBRT after IORT. Twelve patients developed radiologically proved fat necrosis.

Conclusion: The IORT for early stage breast cancer patients using the Intrabeam delivery system was easily implemented in our center with an acceptable toxicity profile and cosmetic outcome.

Saudi Med J 2013; Vol. 34 (11): 1133-1138

From the Departments of Surgery (Merdad, Alghaithy, Al-Thoubaity) and Radiology (Bahadur, Eltaher), King Abdulaziz University Hospital, and Department of Oncology (Fawzy, Hassouna) and Biomedical Physics (Constantinescu), King Faisal Specialist Hospital and Research Centre, Jeddah, Kingdom of Saudi Arabia, and the Department of Radiation Oncology (Hassouna, Eltaher), National Cancer Institute, Cairo University, Cairo, Egypt.

Received 18th June 2013. Accepted 30th September 2013.

Address correspondence and reprint request to: Prof. Yasir A. Bahadur, Department of Radiology, King Abdulaziz University Hospital, PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. Tel. +966 (12) 2401000 Ext. 17444. Fax. +966 (12) 6408047. E-mail: yasirbahadur@hotmail.com

Pathological analysis of breast cancer specimens revealed that up to 90% of microscopic remainders is observed in an area of 4 cm surrounding the macroscopic tumor edge.[1,2] More than 90% of recurrent disease occurring in the breast after breast conserving surgery is within the index quadrant.[3-7,8] Support for the use of accelerated partial breast irradiation (APBI) comes from the observation that 80-90% of local recurrences following whole breast irradiation occurring in proximity to the original tumor bed.[9-11] Thus, irradiation of the immediate vicinity of the primary tumor could be adequate for achieving local control.[12-14] Many methods have been used for PBI like the 3-dimensional conformal radiation therapy (3DCRT), perioperative interstitial multicatheter brachytherapy (BT), endocavitary brachytherapy (MammoSite), and intraoperative radiotherapy (IORT).[3,9,10] Although 3 dimensional analysis of post-mastectomy specimens showed that 63% of breasts harbor occult cancer foci, with 80% of these foci situated remotely from the index quadrant,[12,15] these foci usually remain dormant for many years or even decades, and have a low risk of local recurrence. Retrospective analyses described lower recurrence rates after an additional boost to the tumor bed following whole-breast irradiation with 50 Gray (Gy)/25-28 fractions/5-5.5 weeks. By the additional use of an electron boost of 10-16 Gy (5-8 × 2 Gy), or alternatively interstitial implants (HDR-brachytherapy) local recurrence rates were halved.[16-18] Compared to squamous cell carcinoma (SCC), breast cancer seems to show a different sensitivity toward higher single doses. In 1989, Fowler[19] postulated an α/β ratio of 4 for breast cancer as its best approximation instead of 10 for most SCC. This value was strongly supported by the clinical outcome of Canadian and British Hypo fractionation Trials.[20,21] A lower ratio results in higher sensitivity against higher doses per fraction, an argument clearly in favor of IORT. A major advantage of an immediate boost during surgery is the close proximity of the walls of the surgical cavity because no fluid will artificially enlarge the volume at risk by spherical distension. Another advantage of IORT is the better localization of the tumor bed compared to other techniques guided either by ultrasound (US) or by the surgical scar, which is not always in direct relation to the tumor bed. There are different technical approaches, with the term "IORT" used for the following techniques: a low-kV orthovolt system (Intrabeam) and intraoperative radiotherapy with electrons on mobile, or standard linear accelerators (IOERT). The current study has been carried out using the Intrabeam method of IORT, which consists of a miniature electron-driven low-kV energy x-ray source, emitting an isotropic x-ray spectrum at low energy (50 kV). For breast irradiation, spherical applicators chosen according to the excision cavity's size are put at the top of the source; a point source at the center within a spherical applicator.[22,23] In this paper, we report on our early experience using the Intrabeam radiotherapy delivery system as a modality for IORT in early breast cancer patients.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. This is a prospective phase 2 study carried out at the Department of Surgery and Radiology, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia from December 2010 to November 2012. The institutional review board approved the study, and written informed consent was obtained from every patient. All female patients with biopsy proven invasive duct carcinoma (IDC) and clinical mass ≤3.5 cm, unifocal, unicentric based on radiological data (mammogram+US+MRI) that are eligible for breast-conserving surgery were included. Patients should be available for follow up and competent in this regard. Excision of the breast mass with pathologically proven negative margin (gross examination and frozen section during surgery was performed) and sentinel lymph node dissection was carried out; axillary lymph node dissection (ALND) was completed only when the sentinel node was positive. Frozen section was sent to the pathology lab for evaluation. Patients with adequate surgical margins (not reaching the inked margin) were included; those who needs revision will be included if they turned to have negative margins by wider excision in the same surgical session. Skin-to-surface of applicator distance should be at least 1cm. Subcutaneous tissue flaps were created to accommodate the radio-applicator within the tumor bed and maintain the appropriate skin-to-surface of applicator distance of >one cm. The skin was retracted at least 1 cm from the applicator surface-shaft interface using sterile gauze and sutures (**Figure 1**). Purse string nylon suture was used to fix the lumpectomy cavity around the applicator. After surgically positioning the appropriately sized applicator in the tumor bed and thin lead rubber sheets were used on the surface to minimize radiation scatter (**Figure 2**), radiation is switched on. Radiation dose was prescribed to the applicator surface and delivered using 50 kV x-rays with the Intrabeam miniature X-ray generator

(Carl Zeis Surgical, Oberkochen, Germany). The surface of the tumor bed typically receives a single dose of 20 Gy that attenuates to 5-7 Gy at one cm depth. Patients were then referred to systemic adjuvant chemotherapy (if indicated). External beam radiotherapy (EBRT) to the breast (± supraclavicular/axillary nodes) was given for patients with these features: tumor size >3 cm, lymphovascular invasion (LVI), multifocal lesion/s with area of >3 cm but unicentric, extensive DCIS (>25%, or >3cm), and lymph nodes metastasis. The EBRT was initiated after completion of wound healing and/or 3 weeks from the last day of chemotherapy. Planning has been carried out for 3DCRT after doing CT-simulation in the treatment position. Patients were given 46 Gy/23 fractions /4.5 weeks using 2 tangential breast fields and photons in the range of 6-18 MV. The first follow up visit would be 3 months after radiotherapy, then every 6 months for 5 years, then yearly. During each visit, clinical examination and evaluation of late radiation toxicity will be carried out as per RTOG late radiation toxicity scale.[24] Routine mammography would be ordered every 6 months during the first 2 years, and yearly after that. The MRI has been ordered as per radiologist's request. Other investigations (CT scan or bone scan) will be ordered only when indicated.

All patients' demographics, staging and pathological data were documented and entered as basic patients' characteristics. Treatment related outcome was documented and evaluated in terms of toxicity (acute and late). All statistics were recorded using the Statistical Package for Social Sciences version 11.5 (SPSS Inc, Chicago, IL, USA).

Results. Forty-five female patients with breast cancer were included in this study. **Table 1** show the patient and tumor characteristics. Median age was 54 years (range: 27-79 years) and the majority of them were more than 45 years (n=37; 73.3%). Most of the patients (36 cases; 80%) had tumor <3 cm in diameter, while only 9 cases (20%) had tumor size >3 cm. The majority of cases had pathologically negative axillary lymph node metastases (30 cases; 67%), while only 15 patients (33%) had positive nodes. The median size of the applicators used was 4 cm (range: 3-5 cm). Most of the patients (n=29; 64%) received IORT only, while 16 patients (36%) received EBRT after IORT. Post-operatively, none of the patients developed clinically significant complications as skin breakdown, delayed wound healing, infection needing intravenous antibiotics or surgical intervention, seroma needing aspiration, or hematoma needing surgical evacuation, except one patient (2.2%) developed RTOG grade 3 toxicity (moderate to severe skin erythema). With a median follow-up of 18 months (range, 2-24 months), none of our patients developed local or distant relapse. Twelve patients proved to have fat necrosis on the follow up mammography (5 of them had also MRI, as per radiologist request). Two patients only underwent biopsy of the suspected lesion, and histopathology revealed fat necrosis without evidence of malignant cells. Seven patients developed late radiotherapy skin effect in the form of skin thickening that was evident on radiological imaging. Because of the small number of patients, we could not evaluate the correlation between the incidence of late toxicities and EBRT, IORT applicator size, or tumor size.

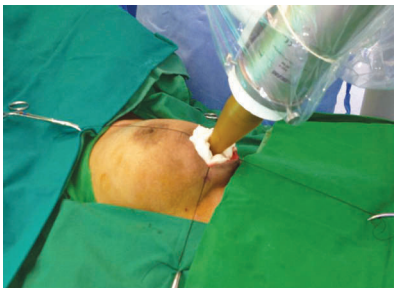

Figure 1 - An Intrabeam applicator inside the tumor bed. The skin was retracted at least one cm from the applicator surface-shaft interface using sterile gauze and sutures.

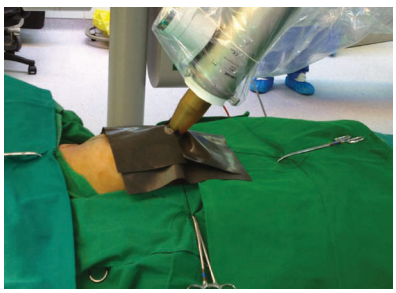

Figure 2 - The Intrabeam applicator inside the tumor bed with thin lead rubber sheets placed on the surface to minimize radiation scatter.

Discussion. One of the largest trials concerning IORT with low-energy x-rays was the TARGIT (targeted intraoperative radiotherapy) trial.[3] In this study, 1113 patients were randomly allocated to targeted IORT and 1119 to EBRT. Out of 996 patients in the IORT group, 854 (86%) received targeted IORT only, and 142 (14%) received targeted IORT plus EBRT. At 4 years, there were 6 local recurrences in the IORT group, and 5 in the EBRT group. Local recurrence in

Table 1 - Patient and tumor characteristics in a study carried out at the Department of Surgery and Radiology, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

Features	n	(%)
Age, years		
Mean ± SD	53.33 ± 12.5	
Range	27-79	
25-<35	6	(13.3)
35-<45	6	(13.3)
45-<55	16	(35.6)
55-65	10	(22.2)
>65	7	(15.6)
Pathologic tumor size, cm		
Mean ± SD	2.3 ± 1.06	
Range	1-5	
<3 cm	36	(80.0)
>3 cm	9	(20.0)
Histopathological type		
Invasive duct carcinoma	42	(93.4)
Invasive lobular carcinoma	2	(4.4)
Other types	1	(2.2)
Histopathological grade		
Grade 1 or 2	38	(84.4)
Grade 3	7	(15.6)
Lymphovascular invasion		
Absent	36	(80.0)
Present	9	(20.0)
Extensive DCIS		
Absent	41	(91.1)
Present	4	(88.9)
Lymph node dissection		
SLND only	30	(66.7)
ALND after SLND	15	(33.3)
Pathologic nodal status		
N0	30	(66.7)
N1	13	(28.9)
N2	2	(4.4)
Estrogen receptor status		
Positive	37	(82.2)
Negative	8	(17.8)
Her2 receptor status		
Positive	6	(13.2)
Negative	39	(86.8)
Intrabeam applicator size		
3 cm	5	(11.0)
3.5 cm	8	(17.8)
4 cm	9	(20.0)
4.5 cm	7	(15.6)
5 cm	16	(35.6)
EBRT after IORT		
Not given	29	(64.4)
Given	16	(35.6)

SD - standard deviation, DCIS - ductal carcinoma in-situ, SLND - sentinel lymph node dissection, ALND - axillary lymph node dissection, EBRT - external beam radiotherapy, IORT - intra-operative radiotherapy

Table 2 - Differences between the results of our study and TARGIT trial[3].

Characteristics	Our study (n=45)	TARGIT trial
Age, years		***(n=1113)***
≤45	11 (24.4)	17 (1.5)
>45	34 (75.5)	1096 (98.4)
Pathological tumor size, cm		***(n=1056)***
≤2	21 (46.6)	912 (86.3)
>2	24 (53.3)	144 (13.6)
LN status		***(n=1059)***
Positive	15 (33.3)	193 (18.2)
Negative	30 (66.6)	866 (81.7)

LN - lymph node, TARGIT - targeted intraoperative radiotherapy

the conserved breast at 4 years was 1.2% (95% CI: 0.53-2.71) in the targeted IORT, and 0.95% (95% CI; 0.39-2.31) in the EBRT group (p=0.41). The frequency of any complications and major toxicity was similar in the 2 groups (for major toxicity, targeted IORT (3.3%) versus EBRT (3.9%), p=0.44). Radiotherapy toxicity (RTOG grade 3) was lower in the targeted IORT group (0.5%) than in the EBRT group (2.1%) (p=0.002). None of our patient developed local recurrence with median follow-up of 18 months, however, longer follow up is needed to report treatment outcome for our patients. In the current study, only toxicity criteria have been evaluated, as the follow-up period is too short to evaluate survival data. Due to cultural issues, evaluation of cosmetic outcome by photography or third party was not allowed. All patients achieved at least acceptable cosmetic outcome according to the patient or physician judgment.

Post-operatively, the TARGIT trial reported clinically significant complications,[3] as skin breakdown or delayed wound healing (2.8%), infection needing intravenous antibiotics, or surgical intervention (2.8%), seroma needing aspiration (2.8%), or hematoma needing surgical evacuation (2.8%), and RTOG grade 3 or 4 toxicities (0.5%). Through our limited experience, none of these complications was reported in our patients, except one patient who developed RTOG grade 3 toxicity. Data still accumulating proving effectiveness of single dose IORT using Intrabeam either in patients having early breast cancer,[3,14,22,23,25] or as a boost.[26-28] Most of the available reports came from centers located outside our region, and concerning patients whose tumor characteristics and biological behavior may differ significantly from ours. As shown by regional investigators, breast cancer among Saudi patients occurs at an earlier age, and more advanced stage than in western countries.[29-31] A median age of 46

years was reported for stage III of breast cancer, which is distinctly different from the 60-65 years median age in Western communities.[30] Recent reviews established that in Arab countries, the average age at presentation of breast cancer is 10 years earlier than in Western countries. Median age at presentation is 48-52 years, with 50% of cases in women younger than 50 years, compared with 25% in developed countries. Due to various socio-economic factors, advanced disease is commonly seen at diagnosis.[32,33] We have also noticed significant differences regarding patients and tumor characteristics between our study and TARGIT trial, as presented in **Table 2**.

Recently, Abulkhair et al[33] suggested several modifications to the current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in breast cancer for use in the Middle East and North Africa (MENA) region, especially those related to risk factor profiles specific to this region. In this regard, the effectiveness of IORT using low kV x-rays should be tested on larger trials, adapted to our patients typical features. It should be mentioned that TARGIT was designed as a randomized, phase 3 trial of partial breast irradiation for selected patients with early breast cancer (T1 and small T2), older than 45 years, and tumor size ≤3 cm. However, we decided to include patients of any age and with tumor size up to 3.5 cm, with the intention to use IORT not only for partial breast irradiation, but also as the optimal technique to deliver a radiation boost to the tumor bed in contrary to other techniques guided by US or the surgical scar. Consequently, the number of patients requiring post-operative EBRT was higher in our study (16/45 [36%]), compared to TARGIT trial (142/996 [14%]). The biological effects of a single high dose of radiation are complex and not yet completely clarified, but it is generally assumed that steep radial dose gradient implies reduced tumor cell control with increasing depth in the tumor bed. Recent biological models analyzing the repair of sublethal lesions during protracted irradiation showed that for the case of Intrabeam, can be defined a "sphere of equivalence," within which the risk of recurrence is equal to that after fractionated EBRT, therefore the increase in local control in the high-dose region near the applicator compensates the reduction of local control at greater distances.[34] In an experimental study, Belletti et al[35] tested the wound fluid collected in the 24 hours interval immediately after lumpectomy, with or without Intrabeam IORT, for its capability to stimulate proliferation and motility of breast cancer cells. They found that while normal wound fluid was stimulatory, fluid collected from patients who received IORT was not, proving that IORT had a beneficial effect. It was assumed that the increased speedy wound healing is the highest in patients below the age of 45, and conventional radiotherapy delivery may be too late to have its effect on tumor microenvironment. Accurately irradiating the tumor beds of young patients with a boost at the right time may give superior results. In older women, the effect of IORT on tumor microenvironment would increase the sphere of equivalence, allowing the omission of EBRT.[35]

This is one of the earliest reports of IORT using the Intrabeam delivery system in the Middle East. This study is limited by the small number of patients and short follows up. We found that the feasibility of this technique and the low complication rate reported in our limited early experience will encourage others to incorporate this treatment modality in their routine radiotherapy practice. As this modality can decrease the treatment time to only one day for patients having early breast cancer, it would considerably help a large number of patients, especially those coming from remote areas seeking radiotherapy treatment. Also, it could significantly decrease the workload on the radiotherapy centers, which are already few in our region.

In conclusion, the IORT using low kV X-rays was easily implemented in our center, with an acceptable toxicity profile. For more robust data regarding toxicity, disease control, and survival, a higher number of patients and longer follow-up is needed.

References

1. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 carcinomas. Implications for clinical trials of breast-conserving surgery. ***Cancer*** 1985; 56: 979-990.
2. Faverly DR, Hendriks JH, Holland R. Breast carcinomas of limited extent: frequency, radiologic-pathologic characteristics, and surgical margin requirements. ***Cancer*** 2001; 91: 647-659.
3. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority phase 3 trial. ***Lancet*** 2010; 376: 91-102.
4. Halsted WS. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. ***Ann Surg*** 1894; 20: 497-555.
5. Fisher B, Bryant J, Dignam JJ, Wickerham DL, Mamounas EP, Fisher ER, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. ***J Clin Oncol*** 2002; 20: 4141-4149.
6. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. ***N Engl J Med*** 2004; 351: 963-970.

7. Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. ***N Engl J Med*** 2004; 351: 971-977.
8. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. ***Ann Oncol*** 2001; 12: 997-1003.
9. Polgár C, Strnad V, Major T. Brachytherapy for partial breast irradiation: the European experience. ***Semin Radiat Oncol*** 2005; 15: 116-122.
10. Vicini FA, Arthur DW. Breast brachytherapy: North American experience. ***Semin Radiat Oncol*** 2005; 15: 108-115.
11. Clarke DH, Le MG, Sarrazin D, Lacombe MJ, Fontaine F, Travagli JP, et al. Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institute Gustave-Roussy. ***Int J Radiat Oncol*** Biol Phys 1985; 11: 137-145.
12. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. ***Br J Cancer*** 1996; 74: 820-824.
13. Baum M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. ***Lancet*** 1997; 349: 208.
14. Vaidya JS, Joseph D, Hilaris BS. Targeted intraoperative radiotherapy (TARGIT) for breast cancer; an international trial. ***Breast Cancer Res Treat*** 2002; 76 (suppl 1): S116.
15. Vaidya JS, Vyas JJ, Mittra I, Chinoy RF. Multicentricity and its influence on conservative breast cancer treatment strategy. Hong Kong International Cancer Congress; Hong Kong; 1995 Nov 17-19.
16. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. ***J Clin Oncol*** 1997; 15: 963-968.
17. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. ***J Clin Oncol*** 2007; 25: 3259-3265.
18. Antonini N, Jones H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. ***Radiother Oncol*** 2007; 82: 265-271.
19. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. ***Br J Radiol*** 1989; 62: 679-694.
20. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, et al. The UK standardisation of breast radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. ***Lancet*** 2008; 371: 1098-1107.
21. Whelan TJ, Kim DH, Sussman J. Clinical experience using hypofractionated radiation schedules in breast cancer. ***Semin Radiat Oncol*** 2008; 18: 257-264.
22. Kraus-Tiefenbacher U, Steil V, Bauer L, Melchert F, Wenz F. A novel mobile device for intraoperative radiotherapy (IORT). ***Onkologie*** 2003; 26: 596-598.
23. Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, et al. Targeted intra-operative radiotherapy (TARGIT): an innovative method of treatment for early breast cancer. ***Ann Oncol*** 2001; 12: 1075-1080.
24. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). ***Int J Radiat Oncol Biol Phys*** 1995; 31: 1341-1346.
25. Deneve LJ, Hoefer AR, Harris RE, Lanorga C. Accelerated partial breast irradiation: A review and description of an early North American surgical experience with the intrabeam delivery system. ***Cancer Control*** 2012; 19: 295-308.
26. Wenz F, Welzel G, Blank E, Hermann B, Steil V, Sutterlin M. Intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage X-rays: the first 5 years of experience with a novel approach. ***Int J Radiat Oncol Biol Phys*** 2010; 77: 1309-1314.
27. Vaidya JS, Baum M, Tobias JS, Wenz F, Massarut S, Keshtgar M, et al. Long-term results of targeted intraoperative radiotherapy (TARGIT) boost during breast-conserving surgery. ***Int J Radiat Oncol Biol Phys*** 2010; 81: 1091-1097.
28. Kraus-Tiefenbacher U, Bauer L, Scheda A, Fleckenstein K, Keller A, Hersking H. Long-term toxicity of an intraoperative radiotherapy boost using low energy X-rays during breast-conserving surgery. ***Int J Radiat Oncol Biol Phys*** 2006; 66: 377-381.
29. Al-Rikabi A, Husain S. Increasing prevalence of breast cancer among Saudi patients attending a tertiary referral hospital: a retrospective epidemiologic study. ***Croat Med J*** 2012; 53: 239-243.
30. Ezzat AA, Ibrahim EM, Raja MA, Al-Sobhi S, Rostom A, Stuart RK. Locally advanced breast cancer in Saudi Arabia: high frequency of stage III in a young population. ***Med Oncol*** 1999; 16: 95-103.
31. Al Shehri S, Abulkhair OAM, Al Kushi A, Musaad S, Al Olayan A, Jazieh AR. Clinical and pathologic profile of breast cancer in a tertiary cancer center in Saudi Arabia. ***J Clin Oncol*** 2011; 29: S1603.
32. Najjar H, Easson A. Age at diagnosis of breast cancer in Arab nations. ***Int J Surg*** 2010; 8: 448-452.
33. Abulkhair O, Saghir N, Sedky L, Saadedin A, Elzahwary H, Siddiqui N, et al. Modification and implementation of NCCN guidelines on breast cancer in the Middle East and North Africa region. ***J Natl Compr Canc Netw*** 2010; 8 (Suppl 3): S8-S15.
34. Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F. Sphere of equivalence - a novel target volume concept for intraoperative radiotherapy using low-energy X-rays. ***Int J Radiat Oncol Biol Phys*** 2008; 72: 1575-1581.
35. Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, et al. Targeted intraoperative radiotherapy (TARGIT) impairs surgical wound-stimulated breast cancer cell proliferation and invasion. ***Clin Cancer Res*** 2008; 14: 1325-1332.