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Postoperative Radiotherapy in Early and Operable Breast Cancer

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Breast radiotherapy (RT) has changed over the passed few decades mainly due to changes in locoregional treatment of the breast cancer and improvements in technology of radiotherapy equipment. It has now become the standard part of the breast conserving procedure, as well as in patients who underwent mastectomy with T3 and/or 4 or more positive nodes in axilla.

In treatment of ductal carcinoma in situ, postoperative RT after lumpectomy is almost always required, because it reduces ipsilateral invasive and DCIS recurrence by approximately 50-60%.

For invasive breast cancer RT decreases the locoregional relapse rate by 70%. The indication for postoperative RT and the definition of the target volumes depend on the prognostic factors and surgical procedures.

The overview by the Early Breast cancer Trialists' Collaborative Group (EBCTCG) demonstrates for the first time, that postoperative RT is not only important in achieving loco-regional control, but also has significant influence on long-term survival. This benefit of postoperative RT is achieved by proper indication of RT and more importantly by using modern RT techniques that can avoid the serious late side-effects.

Keywords. *early breast cancer, postoperative radiotherapy, conservative surgery, mastectomy*

INTRODUCTION

Treatment of early breast cancer is multidisciplinary approach, involving surgery (mastectomy or breast conserving surgery with axillary dissection), postoperative radiotherapy and an increasingly wide spectrum of systemic therapy including hormonal therapy, chemotherapy and targeted therapy.

Randomized trials have established that survival rates after conservative surgery followed breast irradiation are equivalent to those observed after modified radical mastectomy [1]. Moreover, the use of screening mammography has led to a relative increase in small tumors, ideally suitable for breast conservation. As a consequence, the use of conservation surgery has risen progressively during the 1980s and 1990s, with a corresponding increase in the breast irradiation.

Breast radiotherapy (RT) has changed over the passed few decades mainly due to changes in locoregional treatment of the breast cancer and improvements in technology of radiotherapy equipment.

Radiotherapy is, similar to surgery, a local treatment primarily aimed to reduce locoregional failure. Because locoregional failure can result in increased mortality and morbidity, RT is important part of breast cancer treatment.

In the case of breast cancer RT is generally given after conservative surgery or mastectomy, so the target volumes can be the breast or the thoracic wall and/or the regional lymph nodes.

Recent meta-analysis of randomized trials have established that breast cancer mortality can be significantly reduced by locoregional RT, and that the increased intercurrent mortality observed in older trials was caused by an excess in cardiovascular deaths, associated with the earlier techniques of irradiation.

The overview by the Early Breast cancer Trialists' Collaborative Group (EBCTCG) demonstrates for the first time, that postoperative RT is not only important in achieving loco-regional control, but also has significant influence on long-term survival [2]. EBCTCG review confirmed a 75% reduction in local recurrence risk after RT and showed that prevention for every 4 local recurrences at 5 years, will avoid one breast cancer death during the 15 years of follow-up.

This survival benefit is achieved by proper indications of RT and more importantly by using radiotherapy techniques that can avoid the serious late effects to the heart

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and lungs.

BREAST IRRADIATION FOR DUCTAL CARCINOMA IN SITU

Since the introduction of screening mammography, there has been an enormous increase in the detection of ductal carcinoma in situ (DCIS) - about 15-40% of newly diagnosed breast cancers [3,4]. DCIS also known as noninvasive breast cancer, preinvasive breast cancer or intraductal carcinoma is local disease confined to the breast without any ability to produce systemic metastases and with minimal failure after adequate local therapy.

The majority of cases of DCIS (90%-95%) are presented as suspiciously grouped, pleomorphic or fine linear microcalcifications on mammograms, while 5-10% is presented as a palpable mass or nipple discharge [5].

Current treatment for DCIS range from simple tumor excision, to various forms of wider excision (quadrant resection), to mastectomy. All treatments less than mastectomy require postoperative RT.

Mastectomy is a curative treatment for approximately 98%-99% of patients with DCIS [5,6]. But it is also aggressive treatment for most of these patients especially in the era of breast conservative treatment for invasive breast cancer. The recurrence rate after mastectomy for DCIS is 0-2%, so there is no need for adjuvant RT [7].

Conservative surgery for DCIS should result in a low rate of local recurrence and should not lead to higher rates of distant metastases and death compared with mastectomy. However the earlier reports of breast conservation for DCIS without postoperative RT demonstrated that the recurrence rates were high, around 20-30% at 10 years and 50% of recurrences were in the form of invasive disease [6,8].

Radiotherapy dose commonly used is 50Gy to the whole breast. Three big randomized trials evaluated the role of RT after lumpectomy for DCIS: The National Surgical Adjuvant Breast Project (NSABP) protocol B-17, The European Organization for Cancer Research and Treatment (EORTC) protocol 10853 and The United Kingdom, Australia, New Zeeland DCIS trial (UK trial). All of these trials showed that RT reduces ipsilateral invasive and DCIS recurrence by approximately 50-60% but no survival benefit was seen [3,6].

There are many of parameters important in predicting local recurrence in conservative surgery in DCIS, such as: tumor size, nuclear grade, histological type of DCIS, presence of necrosis, surgical margins, age of patients.

The most important risk factor for recurrence is the width of the tumor-free margin. Patients with narrower surgical margins (<1mm) had a higher likelihood of recurrence [5]. Some studies observed a low recurrence risk with clear margins exceeding 10 mm, suggesting that it might be safe to omit RT in that subgroup of patients, but randomized trials indicated that RT reduces local recurrence in all subgroup of patients with DCIS [9]. Presence of necrosis and nuclear grade are also predictors of prognosis indicating higher local recurrence rate in high grade DCIS.

Age of patient at diagnosis was found to be a very important risk factor. Young patients have a higher rate of local recurrence than older patients, especially patients younger than 40 years [6,9]. That fact open a new question which take into consideration to increasing total tumor dose with boost irradiation similar to breast conserving treatment for invasive cancer.

To predict the long-term recurrence risk in breast conserving therapy there is a scoring system called Van Nuys Prognostic index (VNPI) originated by Silverstein [10]. The VNPI assigns patient an overall score which takes into account patient's age, tumor size, width of closest margin and tumor grade. This classification system make possible to select the most appropriate therapy for each patients, in other words to select between mastectomy or conserving surgery with or without postoperative RT. Disregarding the breast preservation is now accepted as a treatment approach for DCIS, there are still patients whose local recurrence rate with breast preservation and postoperative RT is so high that mastectomy is the most appropriate treatment. On the other hand in some patients with good prognostic characteristics treatment by adequate excision alone may be a valid approach.

Therefore, until conclusive randomized evidence allows definition of subgroups in whom RT can be safely omitted, RT should remain part of the standard breast-conserving therapy for all patients with DCIS, as is the case for invasive cancer.

BREAST IRRADIATION AFTER CONSERVATIVE SURGERY FOR INVASIVE CANCER

Today the standard conservative treatment for early invasive breast cancer consists of complete surgical resection of the primary tumor (achieving at least histological clear margins), axillary dissection or sentinel node biopsy and postoperative whole breast radiation therapy and in node-positive patients also regional lymph node irradiation. Tumor dose to the breast is usually 50 Gy in 5 weeks delivered with tangential fields and additional boost of 10-16 Gy to the tumor bed. The purpose of the irradiation is to minimize the risk of local failure and thus improve disease-specific survival without causing side effects to the heart or lungs.

The Meta analysis of EBCTCG showed that postoperative RT after conservative surgery reduced the 5-year local recurrence rate from 26% to 7% while 15-year breast cancer mortality risk was decreased from 35,9% to 30,5% [2].

Since breast recurrences are most often observed within the vicinity of the primary lesion, a localized radiation boost to the tumor bed is frequently recommended. Trials have demonstrated that boost irradiation significantly improves local control compared with whole breast irradiation alone. The "EORTC 22881-10882 boost versus no boost trial" showed that after 50 Gy whole breast irradiation, adding a boost of 16 Gy decreases local recurrence rates by a factor of almost

2 [11,12]. The absolute benefit from boost treatment is particularly marked in young patients. The analysis showed that for patients 35 years of age or less the addition of a boost resulted in reduction of the 5-year local recurrence rate from 26% to 8,5%, while for patients older than 60 years this reduction was only from 3,9% to 2,1% [13].

A boost dose can be delivered with the external beam (single direct field using electron therapy or tangential fields with photons) or with brachytherapy. EORTC boost vs. no boost trial showed that there is no significant differences between three boost techniques (electron, photon and interstitial boost) regarding local control, fibrosis and cosmetic results [11]. Choice of boost technique is likely to depend largely upon the personal preference and training of the radiation oncologist and upon the local infrastructure.

The rational for whole breast irradiation is that it will eliminate possible areas of occult multicentric in situ or invasive cancer in remote areas of the breast. But, approximately 80% of breast cancer recurrences after lumpectomy occur near the original tumor site whether they are treated with excision alone or followed by whole breast irradiation. In addition, a very important reduction in LRF has been observed in older patients (over 55 years), also in the group without postquadrantectomy irradiation. These observations encourage the idea of more limited treatment in order to avoided whole breast irradiation in selected patients with a low risk of recurrence.

Partial breast irradiation (PBI) is a new approach where a single or multiple fractions are given to the excision site and the adjacent tissues in a short period of time. The main advantages of this method are the avoidance of unnecessary side effects, shortening of the overall treatment time and improving the quality of life. PBI includes interstitial brachytherapy (low dose rate or high dose rate), external beam radiotherapy (3D conformal or IMRT) and intraoperative radiotherapy.

IntraOperative Radiation Therapy (IORT) is a special irradiation technique refers to the delivery of a high single radiation dose to the tumor bed during the surgical intervention, after the removal of the tumor mass [14,15]. Modern IORT is carried out with electron beams produced by a mobile linear accelerator with a spectrum of electron energy (3-12 MeV) which can be directly placed in operation room. Besides the reduction in total time of treatment, an important advantages of IORT are the protection of surrounding tissues (heart, lung, skin) and avoidance of the interactions with the systemic therapy.

Another novel approach in irradiating the tissue immediately surrounding the lumpectomy cavity is the MammoSite radiation therapy system [16]. This technique provides a simpler, more assured technique for performing breast brachytherapy. The system consists of balloon applicator which is inserted into the resection cavity immediately after lumpectomy. An HDR Ir-192 source is positioned at the center of the balloon with the planned target volume (PTV) consists of a 1 cm thick spherical shell surrounding the balloon.

Regardless of type of PBI, it is of great important adequate patient selection for PBI. The American Society of Breast Surgeons has proposed a consensus recommendation for PBI based on: patients older than 50 years, T≤ 2 cm, pN0, invasive ductal carcinoma or DCIS and microscopically negative margins.

In spite of very promising first results of PBI in clinical trials, there is still a considerable controversy about the optimal minimum treatment of early breast carcinoma required for adequate local control without compromising the therapeutic effect.

LOCAL RADIOTHERAPY AFTER RADICAL MASTECTOMY

Radical mastectomy was considered for many years as a standard treatment option for operable breast cancer.

Patients currently requiring mastectomy are likely to have larger tumors and positive lymph nodes, and will frequently be candidates for postmastectomy RT (PMRT).

It is well known that postoperative RT after mastectomy reduces locoregional relapse. But recent trial overviews (British Columbia trial, Danish Breast Cancer Cooperative Group – DBCCG 82b trial and DBCCG 82c trial) established conclusively that locoregional RT following ablative surgery not only improves tumor control, but also improves overall survival in appropriate high-risk premenopausal and postmenopausal patients [17,18].

After the result of these three randomized trials of postmastectomy RT published in 1997 there is evidence of increasing in the use of postoperative regional nodal irradiation in node positive patients.

Review of EBCTCG showed that postmastectomy RT in node positive disease reduce 5-year local recurrence risk from 23% to 6%, while 15 year breast cancer mortality was decreased from 60,1% to 54,7%. By contrast in node-negative disease, 5-year local recurrence risk was only 6% even in the absence of RT. Although RT reduces it to 2% there is no significant reduction in 15-year breast cancer mortality [2].

Therefore it is important to identity the patients who could potentially have survival benefit of postoperative RT and on the other hand not offer RT to the patients who are not at increased risk for failure.

One of the most significant predictor for LRF is involvement of the axillary lymph nodes. In general, in patients with 1-3 positive lymph nodes incidence of LRF in the absence of RT was 5-15%, while in patients with 4 of more positive nodes it was 20-50% at 10 years [18].

Tumor size is also important factor for LRF indicating that for node positive T1/2 patients the LRF risk is 12-20% and for T3 is 31-45% [18].

On the basis of the results of randomized trials, American Society of Clinical Oncology (ASCO) guidelines and St Gallen consensus report, PMRT should be recommended to all patient who are at more than 20% risk of loco regional failure at 10 years (node negative

patients with tumor larger than 5 cm or involving the skin or chest wall and all patients with four or more positive nodes) [17,18,19]. Patients with T1-2 tumors and less than four involved axillary nodes generally have LRF rates less than 15% and for that intermediate risk group of patients there was insufficient evidence to recommend PMRT routinely. For this subgroup of patients further research will be required to determine which patients could have sufficient benefit regarding locoregional control or survival to justify PMRT.

There are currently no data supporting the use PMRT in patients with negative axillary nodes, except advanced local tumors [19].

Locoregional irradiation after modified radical mastectomy refers to RT involving the ipsilateral chest wall, as well as the ipsilateral axillary, supra- and infra-clavicular and internal mammary lymph nodes. It is unclear whether all these areas need to be irradiated, but current evidence suggests that the chest wall is probably the critical target for PMRT.

The most common site of locoregional failure (LRF) is the chest wall, so it is nearly always included in target volume of PMRT. Over half of all locoregional recurrences occurred at the chest wall.

Generally accepted indications for RT of exclusively the thoracic wall are tumor invasion of the surgical margins and invasion of pectoral muscle. The skin itself is not part of the target volume, except the locally advanced breast cancer with skin infiltration (T4b-T4d) [13].

The second most common site of LRF is supra and infraclavicular lymph nodes, around 41% of all LRF occurred in this region [18].

The risk of supraclavicular recurrence after mastectomy depends mainly on the extent of axillary involvement. In patients with 1-3 positive axillary nodes, supraclavicular recurrence occur in 1-4% of cases, so there is no strong support to irradiate this region [17]. But in patients with 4 or more positive axillary nodes LRF in supraclavicular nodes was seen in 13-17% of patients who didn't have postoperative RT and in 2-4% in irradiated patients indicating that this region should be irradiated in high risk patients.

The LRF in axilla is extremely rare if complete axillary dissection is performed, regardless of the extent of the axillary involvement. The risk of axillary failure is 2-4% in node positive patients after level I-II axillary dissection [18]. Therefore full axillary RT is not generally recommended following an adequate dissection.

Accepted indications for axillary RT are invasion of the sentinel node without further axillary surgery, when axillary clearance was not complete and when axillary surgery was not performed [13].

The most controversial issue in postoperative RT is irradiation of internal mammary nodes (IMN). Invasion of the IMN varies between 3% and 65% depending on the tumor stage and the position of the primary tumor in the breast [13]. However, a clinically apparent invasion of these nodes is only 2%.

The increasing use of effective systemic chemotherapy and potential serious cardiac morbidity caused by IMN irradiation are reasons of decreasing use of IMN irradiation. Also the increase in breast cancer screening has significantly increased the percentage of patients at low risk for IMN involvement. However, there still remain subsets of patients who are at high risk for IMN involvement like advanced primary disease (T3, T4), advanced nodal disease with central and medial tumors. In this group of patients the benefits of IMN irradiation may outweigh the risks.

Nevertheless, the role of RT of the IMN will be revealed after publishing the results of several prospective trials investigating the value of IMN irradiation.

For patients undergoing reconstruction after mastectomy with prostheses (implants or tissue expanders), most of the evidence suggests that complications are more frequent and cosmesis is poorer with addition of radiation [20]. RT can lead to a hardening of implants by capsular contracture, and leakage or rupture of expanders may occur. RT seems to have no significant effect on the viability and relatively minor effect on the cosmetic outcome of reconstruction with myocutaneous flaps, irrespective of whether RT is given before or after surgery. In general, reconstruction with implants should be avoided where there is a high likelihood of RT being required.

RADIOTHERAPY TECHNIQUE

Technology innovations in the last few decades have lead to great changes in process of RT planning and delivering.

Breast cancer RT is carried out using megavoltage linear accelerators which produce high energy (6-18MV) photons (x-rays) and electrons (in some more complex treatment plans like irradiation of chest wall, and IMN or giving a boost dose to the tumor bed).

Progress in computer technology and application new high-resolutive imaging methods like computed tomography (CT), magnetic resonance (MR) and positron emition tomography (PET) make possible construction of effective computer systems for RT planning, virtual simulation and high-precision conformal radiotherapy.

Until recently standard RT techniques was two-dimensional planning which optimizes dose in a single plane of the breast. Standard RT planning has used a clinical simulator to display the size and shape of treatment fields and arrangements of the treatment beams.

Today it is replaced with three-dimensional (3D) planning with conformal dose delivery and homogeneity throughout the entire target volume. 3D treatment planning make possible to reduce RT exposure to the heart and lungs and reduce side effects to these organs.

Virtual simulation is modification of radiation treatment planning which incorporates a laser positioning system with the computed tomography (CT) scanner and a treatment planning system. It is now replaced clinical simulator.

Further dose optimization was achieved using a new treatment delivering technique called intensity-modulated radiation therapy (IMRT) uses multiple beams with variable intensity. Its advantage lies in the high conformance of radiation to the target, and with careful computer-based planning, healthy tissues can be spared.

In order to compensate respiratory motion during performing radiotherapy a new technique Breathing Adapted Radiotherapy (BART) was introduced. BART implies that the radiation beam is turned on only during pre-specified phase of the respiratory cycle, thus modifying organ motion and position in the field. It was shown that deep inspiration reduces cardiac volume in the radiation field of left-sided breast cancer.

Reducing the volume of lung and heart tissue within the RT field may prevent long-term toxicity for patients received treatment for breast cancer.

CONCLUSION

Postoperative RT has a very important role in multidisciplinary treatment of early breast cancer. Future research will have to investigate the indications for more selective use of adjuvant RT, and use of newer techniques of imaging, treatment planning, and beam delivery for optimizing breast cancer treatment in order to improve target dose homogeneity and better protection of normal tissues, with corresponding reductions in breast fibrosis and other side-effects. This is very important because the overall prognosis for patients with early breast cancer is relatively good, and significant proportion may be expected to live for several decades after successful primary treatment.

REFERENCES

1. Kurtz J. the curative role of radiotherapy in the treatment of operable breast cancer.Eur J Cancer,2002;38:1961-74. http://dx.doi.org/10.1016/S0959-8049(02)00314-3

2. Early Breast Cancer Trialists Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005; 366:2087-2106. PMid:16360786

3. Wood WC. The role of clinical trials in changing therapy for ductal carcinoma in situ. Ann of Surg Oncol. 2003, 11;24S-27S. http://dx.doi.org/10.1007/BF02524792 PMid:15015706

4. Rakovitch E, Pignol JP, Chartier C, Hanna W, Kahn H, Wong J. et al. The management of ductal carcinoma in situ of the breast: a screened population-based analysis. Breast Cancer Res Treat 2007, 101: 335-347. http://dx.doi.org/10.1007/s10549-006-9302-0 PMid:16838110

5. Boughey JC, Gonzales RJ, Bonner E et Kuerer HM. Current treatment and clinical trial developments for ductal carcinoma in situ of the breast. The Oncologist 2007,12;1276-1287. http://dx.doi.org/10.1634/theoncologist.12-11-1276 PMid:18055847

6. Harris JR. Radiotherapeutic considerations for ductal carcinoma in situ. ASCO 2005, Educational Book Manuscript, 69-74.

7. Hwang ES. Ductal carcinoma in situ: Surgical update and future directions. ASCO 2005, Educational Book Manuscript, 80-83.

8. Mansel RE. Ductal carcinoma in situ: Surgery and radiotherapy. The Breast 2003, 12: 447-450. http://dx.doi.org/10.1016/S0960-9776(03)00151-6

9. Bijker N, Meijmen P, Peterse JL, Bogaerts J, Van Hoorebeeck I, Julien JP. et al. Breast conserving treatment with or without radiotherapy in ductal carcinoma in situ: Ten-year results of European organization for research and treatment of cancer randomized phase III trial 10853 – A study by EORTC Breast cancer cooperative group and EORTC Radiotherapy group. JCO 2006, 24(21): 3381-3387. http://dx.doi.org/10.1200/JCO.2006.06.1366 PMid:16801628

10. Silverstein MJ and Buchanan C. Ductal carcinoma in situ: USC/Van Nuys prognostic index and the impact of margin status. The Breast 2003, 12: 457-471. http://dx.doi.org/10.1016/S0960-9776(03)00153-X

11. Poortmans P, Bartelink H, Horiot JC, Struikmans H, Van der Bogaert W, Forquet A. et al. The influence of the boost technique on local control in breast conserving treatment in the EORTC "boost versus no boost" randomized trial. Radiother Oncol 2004; 72:25-33. http://dx.doi.org/10.1016/j.radonc.2004.03.007 PMid:15236871

12. 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. Radiotherapy and Oncology 2007;82:265-271. http://dx.doi.org/10.1016/j.radonc.2006.09.014 PMid:17126434

13. Poortmans P. Evidence based radiation oncology: Breast cancer. Radiotherapy and Oncology 2007;84:84-101. http://dx.doi.org/10.1016/j.radonc.2007.06.002 PMid:17599597

14. Orecchia R, Ciocca M, Lazzari R, Garibaldi C, Leonardi MC, Luini a. et al. Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. Breast 2003; 12:483-90. http://dx.doi.org/10.1016/S0960-9776(03)00156-5

15. Veronesi U. Orecchia R. Luini A. et al. A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are coservatively treated. Eur J Cancer,2001;37:2178-83. http://dx.doi.org/10.1016/S0959-8049(01)00285-4

16. Streter OE, Vicini FA, Keisch M, Astrahan MA, Jozef G, Silverstein M. et al. MammoSite radiation therapy system. Breast 2003; 12:491-96. http://dx.doi.org/10.1016/S0960-9776(03)00157-7