Recent advances in breast cancer radiotherapy: Evolution or revolution, or how to decrease cardiac toxicity?

Youlia M Kirova

Youlia M Kirova, Radiation Oncology, Institut Curie 26, Rue d’Ulm, 75005 Paris, France
Author contributions: Kirova YM solely wrote this paper.
Correspondence to: Dr. Youlia M Kirova, Radiation Oncology, Institut Curie 26, Rue d’Ulm, 75005 Paris, France. youlia.kirova@curie.net
Telephone: +33-1-44324637 Fax: +33-1-44324616
Received: February 6, 2010 Revised: March 1, 2010
Accepted: March 9, 2010
Published online: March 28, 2010

Abstract

Radiation therapy has a major role in the management of breast cancers. However, there is no consensus on how to irradiate and on volume definitions, and there are strong differences in strategies according to different centers and physicians. New treatment protocols and techniques have been used with the principal purpose of decreasing lung and heart toxicity and adapting radiation treatment to patients’ anatomy. There is evidence that indicates internal mammary chain radiotherapy should be used carefully and that high quality techniques should be used for decreasing the dose delivered to the heart. This review of the literature presents the state of the art on breast cancer radiotherapy, with special focus on the indications, techniques, and potential toxicity.

© 2010 Baishideng. All rights reserved.

Key words: Cardiac toxicity; Ejection fraction; Breast cancer; Radiotherapy; Chemotherapy; Herceptin

INTRODUCTION

Adjuvant radiotherapy to the breast plays a significant role in preventing local failure in women with tumorectomy for early stage breast cancer, as well as postmastectomy chest wall irradiation. Following surgery for early breast cancer, breast irradiation decreases the rate of in-breast local recurrence significantly, which has been demonstrated by randomized trials[1]. Results of a meta analysis showed that there were more cardio related deaths in the group of irradiated patients compared with non irradiated patients[2,3], however, in this period old techniques and treatment modalities were used[2]. On the other hand, with new advances in tumor control and long term survival, breast cancer patients have enough time to develop long term complications[3,4]. In some cases, the principal cause of complications is the anti cancer treatment, in others, there is no direct relationship between heart disease and the use of chemotherapy, radiotherapy and/or targeted treatment. Cardiac toxicity represents a multifactorial process with extreme complexity and direct relationship with patients’ anatomy, habits, co morbidities, and risk factors. Also, received treatment, such as anthracycline-based chemotherapy or capecitabine, radiation therapy, hormonal therapy, target treatments such as trastuzumab, can affect cardiac toxicity. Drug-related cardiac toxicity in patients treated with high-dose chemotherapy has been well described for some drugs[4,6]. For others, such as targeted treatment...
with trastuzumab, studies are beginning[7-9]. The question is how to decrease radiation induced cardiac toxicity using modern techniques of radiotherapy and how we can elucidate predictive factors in some patients indicating they are at risk to develop this kind of toxicity.

BREAST IRRADIATION AFTER BREAST CONSERVING SURGERY

Breast conserving radiotherapy uses tangential fields. Any other beam incidence would lead to useless irradiation of the underlying lung and heart[10]. The possibilities and the limits of commonly used techniques for irradiation of breast with two tangential fields in supine position have been discussed in recent years[11-13]. The volume of irradiated lung, heart, and contralateral breast, must be considered. Treatment-related complications include cardiovascular morbidity that can translate into an increased risk of mortality in the long term[11] and chronic radiation-induced pneumonitis. The early and late complications of radiation are directly related to the patient’s anatomy, total dose delivered, fractionation scheme, and radiation technique.

It can be difficult to understand and represent doses received by organs at risk (OAR) (Table 1). An example is given with the French recommendations, showing there is no clear explanation for which parts of the heart can withstand these doses, for example, coronary arteries or the muscle. Every type of treatment is associated with a different kind of toxicity, and more details are needed to report the doses received by different OAR. For example, concerning lung irradiation, there is a question whether suggested doses should be designated to patients with only breast irradiation or breast and lymph node area radiation.

According to some authors, large, pendulous breasts are, in some cases, a contraindication for breast conservation because cosmetic results have been unsatisfactory with increased fibrosis and retraction[12,13]. A number of institutions have reported the use of different techniques to improve the dose distribution within the breast, decrease acute toxicities, decrease the dose to normal tissues and improve the daily reproducibility of women with large breasts[14-21]. Two simple techniques have already been shown to be safe: breast irradiation in a prone position, which is a technique developed in MSCCC, New York, USA, and an isocentric lateral decubitus position founded in the Institute Curie, Paris, France[18-20]. These two techniques were created to prevent lung and heart irradiation. Example of left side breast cancer treated in a lateral decubitus position is given in Figure 1. This treatment is perfectly adapted for breast irradiation only in the elderly, in cases of patients with lung and/or heart co-morbidities, smokers, patients with pendulous breasts, patients treated with chemotherapy, and other specific cases[22]. The limit is that these two techniques are created and adapted to only breast irradiation.

For teams without facilities for using the previously described techniques, new developments are also available[23]. Wedges cannot compensate for the change in breast shape in the cranio-caudal direction. A field reduction is necessary at the breast fold to avoid overdosage and treatment complications in this area. Dose uniformity throughout the whole breast volume can be achieved by using MLC sub-fields that are shaped to the successive isodoses found in the dose distribution[23].

The definition of tumor bed “boost” volume is currently also well defined in numerous papers (Figure 2). New techniques such as pre- and post-operative CT scan image registration are used.

CHEST WALL IRRADIATION AFTER MASTECTOMY AND LYMPH NODE AREAS, INDICATIONS AND NEW TECHNIQUES OF IRRADIATION

The benefit of adjuvant radiotherapy to the chest wall
has been controversial for many years. Published data have shown that radiotherapy regimens produced moderate but definite reductions, not only in breast cancer mortality, but also in overall mortality[25-29]. The benefit of postmastectomy radiotherapy, independently of the effects of systemic treatment, was shown also in studies of the Danish Breast Cancer Cooperative Group and the British Columbia study[25-31]. However, the first meta-analysis report did not find any advantage in overall survival over 10 and 20 years[30]. One explanation is the increase of non-breast cancer deaths, particularly cardiac disease in relation to older irradiation techniques[2].

Table 2 Simplified rules delineate the lymph node areas before conformal radiotherapy treatment

| Supra clavicular region: contouring of the supraclavicular region is guided by the origin of the internal mammary artery |
| Cranial: Thyroid cartilage |
| Caudal: Clavicular head |
| Medial (med): Trachea |
| Posterior (post)-lateral (lat): Anterior scalene muscle |
| Post-med: Carotid artery |
| Infra clavicular region: The infraclavicular region corresponds to lymphatic drainage between axillary vertex and the superior limit of the axillary LN dissection (LND) |
| Cranial: Pectoralis minor |
| Caudal: Sternoclavicular joint |
| Lat: Pectoralis minor (medial side) |
| Med: Clavicle |
| Ant: Pectoralis major |
| Post: Axillary artery |
| Internal mammary chain: The lymph nodes of the IMC are located within the anterior interspaces; they are located either medially or laterally to the vessels and are concentrated in the upper three interspaces |
| Ant: Ant. part of the vascular area |
| Post: The pleura |
| Med: Medial limit of the vascular area |
| Lat: Lateral limit of the vascular area |
| Caudal: Superior side of the 4th rib |
| Cranial: Inferior limit of supra clavicular area |
| Rotter LN or intra pectoral node: situated between: pectoralis major and pectoralis minor at the 2nd interscalatal space |
| Axilla |
| Ant: Pectoralis major & pectoralis minor |
| Post: Subscapularis, teres major and latissimus dorsi |
| Med: Seratus anterior |
| Lat: 5 mm backward the skin |
| Caudal: 4th and 5th ribs |
| Cranial: Inferior limit of infraclavicular volume or “first clip” after sentinel lymph node procedure |

Figure 2 3D reconstruction of boost volume PTV (green) = GTV (red) + CTV clips (yellow), the breast delineation (pink lines) and the relationship between breast volume and boost volume with the cardiac structure[30].

Another revolution in radiotherapy over the last few years is the development of less toxic techniques of irradiation of LN after careful delineation and adaption to the patients’ anatomy[32,47-49] using high performing radiotherapy. Conformal radiotherapy requires definition of target volumes by anatomical limits based on delineation from CT images. Some authors have proposed anatomically based landmarks, specific for breast cancer radiotherapy, to delineate all regional LN[38-43]. Simplified rules of delineation have been developed in our department to delineate lymph node areas before conformal radiotherapy treatment, using easy to find anatomical structures (Table 2 and Figure 3).

CARDIAC TOXICITY RELATED TO CHEMOTHERAPY, TARGETED TREATMENTS, HORMONAL THERAPY

Other adjuvant treatments for breast cancer have been shown to be cardiotoxic. The principal chemotheraphy in treatment of breast cancer is still anthracycline-based chemotherapy and the toxicity of this chemotherapy is well...
known and documented\textsuperscript{[4-6]}]. The principal example comes from assessment of cardiac status in long-term survivors of pediatric malignancies who received chemotherapy, including anthracyclines. Steinherz et al\textsuperscript{[3]} have studied 201 patients who had received a total anthracycline dose of 200 mg/m\textsuperscript{2} to 1275 mg/m\textsuperscript{2} (median, 450 mg/m\textsuperscript{2}), and 51 patients had mediastinal radiotherapy. The overall incidence and severity of abnormal systolic cardiac function were determined for the entire cohort. Risk factors of total anthracycline dose, mediastinal radiotherapy, age during treatment, and length of follow-up were examined. Twenty-three percent (47/201) of the cohort had abnormal cardiac function on noninvasive testing at long-term follow-up. Correlation between total cumulative dose, length of follow-up, and mediastinal irradiation with incidence of abnormalities was significant. Fifty-six patients were followed up for 10 years or more (median, 12 years), with a median anthracycline dose of 495 mg/m\textsuperscript{2}. Thirty-eight percent (21/56) of these patients, compared with 18\% (26/145) of patients evaluated after less than 10 years, had abnormal findings. Sixty-three percent of patients followed up for 10 years or more after receiving 500 mg/m\textsuperscript{2} or more of anthracyclines had abnormal findings. Nine of 201 patients had late symptoms, including cardiac failure and dysrhythmia, and three patients died suddenly. Microscopic examination of the myocardium on biopsy and autopsy revealed fibrosis. This study illustrates the importance of evaluation of all received treatments and not only one isolated treatment modality.

Other treatments, such as capecitabine, cyclophosphamide, trastuzumab, have also shown cardiac toxicity. Provided that the technique is adapted, the acute skin and heart toxicities of the concomitant administration of trastuzumab-RT appeared satisfactory\textsuperscript{[3]}. There is a trend towards cardiac toxicity in patients with a past history of low ejection fraction, although seemingly poor cardiac risk patients may fare well with high doses of chemotherapy if carefully selected with the aid of a thorough cardiac evaluation with electrocardiogram and cardiac ultrasound. Currently, in our department, in the case of concomitant systemic treatment and radiotherapy, left ventricular ejection fractions, assessed at baseline, before start of RT, after completion of RT and then every 4-6 mo with either echocardiography or multiple gated acquisition scanning, were considered normal if \( \geq 50\% \) or stated so by the cardiologist. At the same time, other risk factors, such as obesity, known cardiac and vascular dysfunction and smoking history must be evaluated.

CONCLUSION

Improvements in breast cancer radiotherapy in the last few years have been spectacular. This fact probably will result in decreasing the side effects of radiation treatment and will improve the quality of life of treated patients with lower rates of side effects. At the same time, the evaluation of long term side effects of new systemic treatments, such as chemotherapy, new targeted drugs, and hormonal treatments, is needed.

ACKNOWLEDGMENTS

To all on the team of breast cancer radiotherapy (Fourquet A, Fournier-Bidoz N, Campana F, Boller M, Dendale R, Castro Pena P, Peurien D, Lelievre H, Stilhart A, Brunet Y).

REFERENCES

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, Mackinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y. 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 randomised trials. Lancet 2005; 366: 2087-2106
2. Darby S. The Early Breast Cancer Trialists’ Collaborative
Kirova YM. Recent advances in breast cancer radiotherapy

Group (EBCTCG): Late complications of radiation therapy, ESTRO Course: Multidisciplinary management of breast cancer. Lisbon, 2009

Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol 2005; 6: 557-565

Brockstein BE, Smiley C, Al-Sadir J, Williams SF. Cardiac and pulmonary toxicity in patients undergoing high-dose chemotherapy for lymphoma and breast cancer: prognostic factors. Bone Marrow Transplant 2000; 25: 885-894

Gianni L, Norton L, Wolmark N, Suter TM, Bonadonna G, Hortobagyi GN. Role of anthracyclines in the treatment of early breast cancer. J Clin Oncol 2009; 27: 4798-4808

Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991; 266: 1672-1677

Alm El-Din MA, Bellon JR, Strom EA, Bourgier C, Jagsi R, Niemierko A, Marsiglia H, Pierle L, Buchholz TA, Taghian AG. Radiation treatments may contribute to the development of cardiac dysfunction in breast cancer patients treated with chemotherapy and trastuzumab. Int J Radiat Oncol Biol Phys 2008; 72: 589-590

Kirova YM, Causa L, Granger B, Savignoni A, Dendale R, Campana F, Tournat H, Pierle JY, Fourquet A, Bollet MA. [Monocentric evaluation of the skin and cardiac toxicities of the concomitant administration of trastuzumab and radiotherapy] Cancer Radiother 2009; 13: 276-280

Bellon JR, Gover MT, Burstin HJ, Harris JR, Harris LN. Concurrent trastuzumab and radiation therapy (RT) in the adjuvant treatment of breast cancer. Int J Radiat Oncol Biol Phys 2005; 63: 555-556

Halperin EC, Perez CA, Brady LW, Wazer DE. Principles and practice of radiation oncology. Lippincott Williams & Wilkins, 2008

Krasin M, McCaill A, King S, Olson M, Emami B. Evaluation of a standard breast tangent technique: a dose-volume analysis of tangential irradiation using three-dimensional tools. Int J Radiat Oncol Biol Phys 2000; 47: 327-333

Leonardi MC, Brambilla MG, Zurridda S, Intra M, Frasson A, Severi G, Robertson C, Orecchia R. Analysis of irradiated lung and heart volumes using virtual simulation in postoperative treatment of stage I breast carcinoma. Tumori 2003; 89: 60-67

Lu QX, Sullivan S, Eggleson T,Holupka E, Bellerive M, Abner A, Lamb CC, Lee A, Stevenson MA, Recht A. A three-field breast treatment technique with precise geometric matching using multileaf collimator-equipped linear accelerators. Int J Radiat Oncol Biol Phys 2003; 55: 1420-1431

Harris JR, Levene MB, Svensson G, Hellman S. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys 1979; 5: 257-261

Prosnitz LR, Goldenberg IS, Harris JR, Hellman S, Danoff BF, Kramer S, Wallner PE, Brady LW. Radiotherapy for carcinoma of the breast instead of mastectomy. An update. Front Radiat Ther Oncol 1983; 17: 69-75

Cross MA, Elson HR, Aros BN. Breast conservation radiation therapy technique for women with large breasts. Int J Radiat Oncol Biol Phys 1989; 17: 199-203

Mazonakis M, Varveris H, Damlakis J, Theoharopolous N, Courtsoyiannis N. Radiation dose to conceptus resulting from tangential breast irradiation. Int J Radiat Oncol Biol Phys 2003; 55: 386-391

Grann A, McCormick B, Chabner ES, Gollamudi SV, Schupak KD, Mychalczak BR, Heerdt AS, Merchant TE, Hunt MA. Prone breast radiotherapy in early-stage breast cancer: a preliminary analysis. Int J Radiat Oncol Biol Phys 2000; 47: 319-325

Merchant TE, McCormick B. Prone position breast irradiation. Int J Radiat Oncol Biol Phys 1994; 30: 197-203

Campana F, Kirova YM, Rosenwald JC, Dendale R, Vilcoq JR, Dreyfus H, Fourquet A. Breast radiotherapy in the lateral decubitus position: A technique to prevent lung and heart irradiation. Int J Radiat Oncol Biol Phys 2005; 61: 1348-1354

Fournier-Bidou N, Kirova Y, Campana F, El Barouky J, Zefkili S, Dendale R, Bollet MA, Mazal A, Fourquet A. Technical alternatives for breast radiation oncology: Conventional radiation therapy to tomotherapy. J Med Phys 2009; 34: 149-152

Bollet MA, Campana F, Kirova YM, Dendale R, Salieu MG, Rosenwald JC, Fourquet A. Breast radiotherapy in women with pectus excavatum (funnel chest): is the lateral decubitus technique an answer? A dosimetric study. Br J Radiol 2006; 79: 785-790

Vicini FA, Sharpe M, Kestin L, Martinez A, Mitchell CK, Wallace MF, Matter R, Wong J. Optimizing breast cancer treatment efficacy with intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2002; 54: 1336-1344

Kirova YM, Fournier-Bidou N, Servois V, Laki F, Pollet GA, Salmon R, Thomas A, Dendale R, Bollet MA, Campana F, Fourquet A. How to boost the breast tumor bed? A multidisciplinary approach in eight steps. Int J Radiat Oncol Biol Phys 2008; 72: 494-500

Gebski V, Lagleva M, Keech A, Simes J, Langlands AO. Survival effects of postmastectomy adjuvant radiotherapy using biologically equivalent doses: a clinical perspective. J Natl Cancer Inst 2006; 98: 26-38

Overgaard M, Hansen PS, Overgaard J, Rose C, Andersen M, Bach R, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997; 337: 949-955

Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersen M, Kambly C, Kjaer M, Gadeberg CC, Rasmussen BB, Blicher-Toft M, Mouridsen HT. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999; 353: 1641-1648

Razaj J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, Wilson KS, Knowling MA, Coppin CM, Paradis M, Coldman AJ, Olivotto IA. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997; 337: 956-962

Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, Peto R, Baum M, Fisher B, Host H. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994; 12: 447-453

Pierce LJ. The use of radiotherapy after mastectomy: a review of the literature. J Clin Oncol 2005; 23: 1706-1717

Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, Fleming GF, Formenti S, Hudis C, Kirshner JJ, Krause DA, Kuske RR, Langer AS, Sledge GW Jr, Whelan TJ, Pfister DG. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19: 1539-1569

Gaffney DK, Prows J, Leavitt DD, Egger MJ, Morgan JG, Stewart JR. Electron arc irradiation of the postmastectomy chest wall: clinical results. Radiother Oncol 1997; 42: 17-24

Gaffney DK, Leavitt DD, Tsodikov A, Smith L, Watson G, Patton G, Gibbs FA, Stewart JR. Electron arc irradiation of the postmastectomy chest wall with CT treatment planning: 20-year experience. Int J Radiat Oncol Biol Phys 2001; 51: 994-1001

Magee B, Ribeiro GG, Williams P, Swindell R. Use of an electron beam for post-mastectomy radiotherapy: 5-year
Kirova YM. Recent advances in breast cancer radiotherapy

follow-up of 500 cases. Clin Oncol (R Coll Radiol) 1991; 3: 310-314

35 Hehr T, Budach W, Paulson F, Gromoll C, Christ G, Bamberg M. Evaluation of predictive factors for local tumour control after electron-beam-rotation irradiation of the chest wall in locally advanced breast cancer. Radiother Oncol 1999; 50: 283-289

36 Feigenberg SJ, Price Mendenhall N, Benda RK, Morris CG. Postmastectomy radiotherapy: patterns of recurrence and long-term disease control using electrons. Int J Radiat Oncol Biol Phys 2003; 56: 716-725

37 Gez E, Assaf N, Bar-Deroma R, Rosenblatt E, Kuten A. Postmastectomy electron-beam chest-wall irradiation in women with breast cancer. Int J Radiat Oncol Biol Phys 2004; 60: 1190-1194

38 Kirova YM, Campana F, Fournier-Bidoz N, Stilhart A, Dendale R, Bollet MA, Fourquet A. Postmastectomy electron beam chest wall irradiation in women with breast cancer: a clinical step toward conformal electron therapy. Int J Radiat Oncol Biol Phys 2007; 69: 1139-1144

39 Campana F, Kirova YM, Zervoudis S, Assi H, Fournier-Bidoz N, Dendale R, Iatrakis G, Bollet M, Kyrigios G, Peitsidis P, Fourquet A. Postmastectomy electron-beam chest wall irradiation in women with breast cancer: early and late complications. Gyneco Ro 2007; 3: 170-173

40 Kirova YM, Castro Pena P, Dendale R, Servois V, Bollet MA, Fournier-Bidoz N, Campana F, Fourquet A. Simplified rules for everyday delineation of lymph node areas for breast cancer radiotherapy. Br J Radiol 2009; Epub ahead of print

41 Kirova YM, Castro Pena P, Dendale R, Campana F, Bollet MA, Fournier-Bidoz N, Fourquet A. [Definition of nodal volumes in breast cancer treatment and segmentation guidelines] J Radiol 2009; 90: 747-751

42 Kirova YM, Servois V, Campana F, Dendale R, Bollet MA, Laki F, Fournier-Bidoz N, Fourquet A. CT-scan based localization of the internal mammary chain and supra clavicular nodes for breast cancer radiation therapy planning. Radiother Oncol 2006; 79: 310-315

43 Madu CN, Quint DJ, Normolle DP, Marsh RB, Wang FY, Pierce LJ. Definition of the supraclavicular and infraclavicular nodes: implications for three-dimensional CT-based conformal radiation therapy. Radiology 2001; 221: 333-339

44 Martinez-Monge R, Fernandes PS, Gupta N, Gahbauer R. Cross-sectional nodal atlas: a tool for the definition of clinical target volumes in three-dimensional radiation therapy planning. Radiology 1999; 213: 815-828

45 Castro Pena P, Kirova YM, Campana F, Dendale R, Bollet MA, Fournier-Bidoz N, Fourquet A. Anatomical, clinical and radiological delineation of target volumes in breast cancer radiotherapy planning: individual variability, questions and answers. Br J Radiol 2009; 82: 595-599

S- Editor Cheng JX  L- Editor Lutze M  E- Editor Zheng XM