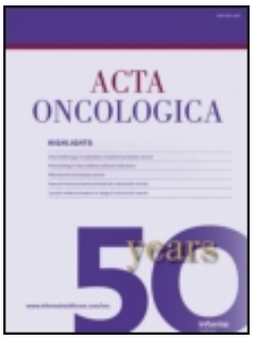

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ORIGINAL ARTICLE

The potential of proton beam radiation therapy in breast cancer

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Abstract
A group of Swedish oncologists and hospital physicists have estimated the number of patients in Sweden suitable for proton beam therapy. The estimations have been based on current statistics of tumour incidence, number of patients potentially eligible for radiation treatment, scientific support from clinical trials and model dose planning studies and knowledge of the dose-response relations of different tumours and normal tissues. In primary breast cancer, it is estimated that about 300 of the annually 3 425 irradiated patients can potentially be candidates for proton beam therapy to reduce late toxicity, mainly from the heart and lungs.

Breast cancer, at 6 500 new cases annually, is the second most common cancer diagnosis in Sweden [1]. The median age is relatively low, namely 62. Radiotherapy has an established role in the primary treatment, partly to reduce the risk of recurrence after breast-preserving surgery for early cancer, and also to reduce the risk of loco-regional recurrence and improve survival in addition to general cytostatic or hormonal treatment for lymph node-positive or locally advanced breast cancer [2]. Analyses of clinical trials and meta-analyses have demonstrated that the ratio between the number of loco-regional failures avoided and breast cancer deaths prevented is between 4 and 5:1 [3–7]. Both loco-regional control and survival was improved by post-mastectomy radiation after neo-adjuvant chemotherapy and mastectomy for locally advanced breast cancer, according to a retrospective analysis of several prospective trials [8].

The overwhelming majority of women with breast cancer are operated on, primarily as a rule or, in the event of locally advanced disease or inflammatory cancer, after preoperative treatment. Surgery is frequently followed by supplementary treatment in the form of radiation, cytostatics or hormones. Estimates and guidelines of the appropriate evidence-based use of radiation therapy for primary breast cancer have been published [2,9–11]. A survey performed by the Swedish Council on Technology Assessement in Health Care, the SBU-report, over 12 weeks in the autumn of 2001 showed radiotherapy against the primary tumour region being given to 822 breast cancer patients [12]. On an annual basis this means about 3 425 patients irradiated, post-operatively as a rule.

Breast cancer irradiation

The volumes irradiated comprise either the remaining breast or occasionally only the surgical bed plus a limited margin after breast-conserving surgery [13], the operation area following mastectomy, one or more regional lymph node stations, i.e. axilla, supra- and infraclavicular glands and parasternal glands or a combination of breast/operation area and lymph node stations. The volumes irradiated vary a great deal in size and shape, depending on the patient's appearance and the tumour location. It can be technically difficult to achieve homogeneous dose distribution in the volumes where cancer cells may be present, while at the same time keeping the dose to adjacent organs low enough to avoid side-effects.

One very common target absorbed dose after both conservative- and radical breast surgery is 25 fractions of 2 Gy, total dose 50 Gy. Sometimes a slightly

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higher fraction dose is given for a period of less than five weeks to a final dose corresponding to a total dose of 50 Gy for five weeks. Boost treatment against the operation area also occurs.

Late side-effects of breast cancer irradiation

The side-effects mainly seen after breast cancer irradiation are pneumonitis, effects on the heart, arm oedema, sometimes in combination with decreased range of motion, breast skin fibrosis, rib fracture and secondary malignancies, mainly contralateral cancer. Effects on the nervous system can also be seen [14].

Many studies have shown increased cardiac mortality following breast cancer irradiation [6,15–18]. The augmentation of risk is confined to mainly left-sided breast cancer and is clearly technique-related. Treatments, in which a larger portion of the heart receives a radiation dose as happened in some earlier studies, entail greater risk than when the irradiated heart volume can be limited. There are modern studies in which no augmented risk of cardiac death was observable for up to ten years [19]. A study based upon the SEER Registry could not find any difference in mortality from ischemic heart disease at 15 years between women with left- and right-sided breast cancer treated between 1985 and 1989 whereas this was seen for those diagnosed between 1973 and 1989 [20]. The absolute risk, however, is relatively limited, which calls for major studies, and excess mortality is mainly observable after ten years [18].

In the meta-analysis of survival following irradiation for early breast cancer [6], a total survival gain of 1.2% (from 35.9 to 37.1%) is noted after 20 years, the corresponding gain after ten years being 2.1% (from 54.5 to 56.6%). After 20 years the proportion of breast cancer deaths has fallen from 51.4% to 46.4%, i.e. an absolute difference of 4.8%, at the same time as the number of deaths from non-breast cancer has risen from 26.2 to 30.5%, or by 4.3% in absolute terms. Many of these studies gave radiotherapy which imposed an unnecessary load on the heart, and it is reasonable to suppose that today's conventional radiotherapy entails less risk of death from other causes especially when the target is defined manually and followed by an individualized dose-planning. Today there are techniques with breathing-adapted radiotherapy with voluntary inspiration which can consistently reduce the dose to both the heart and lungs, most likely reducing the risk for late cardiac and pulmonary toxicity [21]. The magnitude of the excess risk with modern conventional irradiation cannot be reliably stated, but since the absolute reduction of breast cancer deaths achieved with post-operative irradiation is limited, albeit clinically meaningful, the increased mortality from other causes must be very low or close on zero.

Pulmonary complications in the form of acute radiation pneumonitis and late lung fibrosis have also been reported from several studies [22–25]. The risk of pulmonary complications depends on the radiation load on the underlying lung parenchyma and, accordingly, the radiotherapy technique used. In this respect, the risks do not differ appreciably between left and right-sided lung cancer. Pulmonary complications can be troublesome for the patients, but do not have such grave implications as heart complications.

Dermatological side-effects in the form of discoloration, telangiectasias, fibrosis and, in serious cases, necrosis, have also been observed following irradiation of breast cancer. These too depend on radiation load and, accordingly, are technique-related. Photons compared with electrons give a lower load on the skin (at the same time as photons give a larger in-depth dose contribution). It has been estimated that a dose of 50 Gy to the surface of the skin in an area of 150 cm^2 leads to a 2% risk of necrosis [26]. Dermatological side-effects are rarely serious, but they should be avoided because they entail a cosmetically inferior result [27]. Conventional present-day techniques generally have good cosmetic outcomes.

Problems of arm lymph oedema, reduced shoulder mobility and nervous effects from the plexus brachialis are common after surgery to the armpit and post-operative irradiation [28]. Good surgical technique and homogeneous dose distribution are important for limiting these complications. Analyses have shown that overdosage entails not only an increased risk of complications but also better tumour control [29]. This latter indicates that a homogeneous and sufficiently high radiation dose is necessary in the whole of the target.

After all radiation there is a risk of increased induction of secondary malignancies [30]. In the case of breast cancer irradiation, it is above all the risk of contralateral breast cancer that has been observed [31]. The risk of secondary malignancies cannot be firmly quantified, but unnecessary irradiation of non-cancerous tumour should be avoided. In the case of secondary malignancies, this also applies to radiation in low doses which cannot be expected to have other negative effects. It is poorly known whether the hypersensitivity to low doses described for other effects also applies to the induction of malignancies [32]. The risk of secondary malignancies is especially important in connection with intensity modulated radiotherapy (IMRT), since

more often than not many beams are given with increased low dose load to larger volumes of tissue [33].

Clinical experience of proton beam therapy for breast cancer

To our knowledge, no proton beam radiotherapy has been given against a primary breast cancer, the reason being that, classically, small targets near risk organs have been judged the most suitable proton radiation targets. This view, however, is now being revised, and several writers have in fact proposed that the benefit of protons also applies to larger irregular targets where there is a possibility of reducing the dose delivered to other organs [34,35]; see also below.

Model studies

Owing to the difficulty of adequately covering cancer cell containing volumes with a homogeneous radiation dose while at the same time limiting the dose delivered to other organs, a number of different model studies have been undertaken over the years, to evaluate different techniques on patients. These techniques have gradually become more and more sophisticated. A treatment based on three-dimensional dose planning generally achieves better results than when "the fields are inserted by hand". Since, however, 3D dose planning is more labour intensive, various guidelines have been defined as to when a more sophisticated technique is judged necessary also at stage I for irradiation of remaining breast only (e.g. [36]). In cases where the lymph node stations are also included, there is a consensus regarding the need for 3D dose planning [37]. Several studies in recent years have shown IMRT to give better dose distribution, both when the breast only is irradiated [38,39] and when lymph node stations are also included [40,41].

Two studies compared protons with IMRT and a conventional irradiation for gland-positive breast cancer [42,43]. Both studies show IMRT to give better dose distribution and less risk of complications than a 3D-planned photon/electron plan. Johansson et al. [42] studied 11 patients with left-sided gland-positive breast cancer. The target included remaining breast and all lymph node stations. Comparisons of physical dose distribution show protons to give a better and more homogeneous dose distribution to the target, at the same time as the load on adjacent tissue is reduced. At a dose of 50 Gy the risk of cardiac mortality according to a normal tissue complication probability (NTCP) model declined from 6.7% with a tangential technique and 2.2% and 2.1% respectively for IMRT and a conventional photon/electron technique to 0.5% with protons. The risk of pneumonitis declined from about 15% with the best conventional irradiation technique to 0.6% for protons. The proton therapy was given as passively distributed beams with a single field and with no attempt at further optimisation.

In the second work by Lomax and co-workers [44], one patient was studied. The target was equivalent to that in the first studies, and so was the radiation dose, 50 Gy. Only a physical comparison was made. Two IMRT plans were implemented, with attempted maximum optimisation in one of them. The protons were given with 2 fields and conventional "forward" planning but with spot scanning technique. Thus the proton planning was appreciably more sophisticated than in the work by Johansson et al. Compared with the IMRT plans, the protons give better coverage of the target, comparable dose to the left lung but reduced dose to the heart, the other lung and the other breast. The further attempts made at optimising the IMRT plans resulted in it being possible to achieve either the same dose homogeneity as with protons or the same saving on dosage to the lung and heart, but not both. Since only one case was included and no attempt was made to calculate biological effects, reduction of the risk of complications cannot be quantified on the basis of this study.

Summing up, both these studies show that with protons it is possible to give better coverage of the whole target, while at the same time reducing the dose load on other risk organs. This ought to mean less risk of both cardiac mortality and pneumonitis and secondary malignancy induction. Tumour control should be higher as well, though the difference is unlikely to be clinically meaningful. The risk of problems affecting the nervous system and shoulders can also, theoretically speaking, be lower with protons, due to the greater homogeneity of the target.

Assessment of the number of cases eligible for proton beam therapy

If protons were commonly used and not more expensive than conventional irradiation, then in principle all breast cancer patients could be primarily treated with them. Compared with photons/electrons, conventionally or as IMRT, this would mean less risk of serious complications, at the same time as the risk of dermatological side-effects would be unchanged or possibly slightly greater, since protons do not save on the skin dose in the same way as photons do.

The estimate given below of the number of cases presupposes that protons are only used when radiotherapy is given for both remaining breast parenchyma and all lymph node stations in left-sided breast cancer. Treatment of this kind is at present routine in many places, since many clinical studies and meta-analyses of the same have shown considerable reduction of the risk of local recurrence and a slight increase in total survival.

According to the SBU report, in which breast cancer treatments account for 24% of all radiotherapy treatments in the survey, 822 patients received therapy for the primary tumour, which, as indicated above, gives 3 425 patients in Sweden on an annual basis [12]. Of the radiation treatments given, 49% were for stage II, 6% stage III and the remainder stage I. Protons are primarily indicated only for left-sided breast cancer in stages II and III, although the risk of pneumonitis is also reduced in right-sided breast cancer. Given 1 640 left-sided breast cancers, it is estimated that 900 have stages II and III. About 600 of these are under 70 years old, and of these about 300 have undergone breast-conserving surgery. Thus we estimate that 300 patients should be potentially eligible for proton therapy in the first instance. On the basis of the model studies performed, comparing protons with IMRT, IMRT with conventional techniques and various conventional techniques with each other [36,38–43,45], the risk of serious heart complication can be estimated to decline from about 2–3% with IMRT to less than 0.5% with protons. The absolute levels are uncertain, due to these estimates being based on models. The risk appears correlated with the "maximum heart distance", i.e. the maximum distance from the heart contour to field/block edge in a beam's-eye view [36,39]. If MHD is less than 10 mm, the risk of NTCP in the heart is estimated at less than 1%, while for 20 mm it is about 3% and for 30 mm about 5%, after which it rapidly rises with increasing distance [39]. Of special interest to study are the effects on late cardiac and pulmonary toxicity between proton- and breathing adapted radiotherapy following breast-conserving surgery.

It is possible that future choices between conventional technique (IMRT included) and protons are not to be based, as a matter of standard procedure, on the target to be given but on each individual patient's plan, allowing for such measurements as MHD, maximum lung distance or volume of risk organs. The number of breast cancer patients then eligible for a certain technique, e.g. protons, is not known at present. Clinical experience suggests that a figure of 300 patients remains relevant (deduced from an estimate that protons are indicated if NTCP heart is put at 3% or more). If lung toxicity is also included, the number of cases eligible for protons may increase still further.

Cost-benefit estimates

The cost-effectiveness of proton beam therapy has been compared with that of conventional therapy in one study [46]. In the basic assumption, 55-year-old women with left-sided breast cancer have been post-operatively irradiated to 50 Gy. Tumour control is unaffected, but the risk of serious cardiac toxicity is reduced by 76% and the risk of pneumonitis by 96%. If the risk of cardiac toxicity after conventional irradiation is 1.5% and the risk of pneumonitis 14%, the cost per quality-adjusted life year gained (QALY) will be SEK 550 000. For the group of patients where the risk of cardiac toxicity exceeds 3%, averaging 3.5%, the cost per QALY comes to SEK 202 000. The number of cases judged eligible for proton beam therapy is based on this latter group.

Research needed

Further comparative dose planning studies will be needed and also better knowledge concerning the absolute risks of different kinds of toxicity, particularly cardiac/pulmonary toxicity, and the risk of secondary malignancies from various dose loads. Further long-term follow-up of different clinical studies may possibly help to augment knowledge of this kind over the next five years. Ongoing or recently completed clinical studies will also provide better knowledge of the target volumes and target doses needed at different stages and for different tumour characteristics. The benefit of e.g. irradiating the internal mammary lymph nodes is much debated [47–49]. Studies using different cytostatic drugs and other tumour medicines, e.g. trastuzumab [50], can also have a bearing on future radiotherapy. Since some of these medicines are cardio-toxic, their increasing use in primary therapy may entail greater demands for a reduction of radiation loads on the heart or lung [51]. Pilot studies of patients should also be able to commence, primarily in order to study acute toxicity, e.g. in the skin, at existing proton beam therapy centres the world over.

When a facility is clinically operative, all patients must be treated in prospective protocols with insistence on careful long-term follow-up. NCTP must be calculated for various side-effects as compared with the best conventional technique. It is not possible to undertake a randomised study to ascertain any increased tumour control, because this is already very high and the differences between protons and other techniques are probably small. Nor is

it reasonable to start a randomised study with a view to seeing whether cardiac toxicity can be reduced after, say, 15 years. The need, rather, is for various intermediary endpoints to evaluate the risk of subsequent serious toxicity. Various heart studies, e.g. scintigraphy using ^{99m}Tc-sestamibi [52,53], can reflect radiation load, but their relevance to assessing the risk of serious cardiac toxicity is limited.

Summary assessment

It is estimated that in the first instance 300 Swedish patients annually may be eligible for proton beam therapy, given the possibility. The risk of heart/lung complications and the risk of secondary malignancy should then be reduced to very low levels. The treatment cost per patient, with a risk of cardiac toxicity more than 3%, is estimated at some SEK 200 000.

References

[1] Cancer Incidence in Sweden. Epidemiologiskt Centrum 2003;www.sos.se.

[2] Rutqvist LE, Rose C, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in breast cancer. Acta Oncol 2003;42:532–45.

[3] Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337:956–62.

[4] Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997;337:949–55.

[5] Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641–8.

[6] Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000;355:1757–70.

[7] Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 2000;18:1220–9.

[8] Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 2004;22:4691–9.

[9] Foroudi F, Tyldesley S, Walker H, Mackillop WJ. An evidence-based estimate of appropriate radiotherapy utilization rate for breast cancer. Int J Radiat Oncol Biol Phys 2002;53:1240–53.

[10] Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1539–69.

[11] Truong PT, Olivotto IA, Whelan TJ, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy. CMAJ 2004;170:1263–73.

[12] Möller TR, Brorsson B, Ceberg J, Frodin JE, Lindholm C, Nylen U, et al. A prospective survey of radiotherapy practice 2001 in Sweden. Acta Oncol 2003;42:387–410.

[13] American Society of Breast Surgeons. Consensus statement for accelerated partial breast irradiation. Bethesda, MD: American Society of Breast Surgeons; 2003 April 30.

[14] Meric F, Buchholz TA, Mirza NQ, Vlastos G, Ames FC, Ross MI, et al. Long-term complications associated with breast-conservation surgery and radiotherapy. Ann Surg Oncol 2002;9:543–9.

[15] Host H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer–long-term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986;12:727–32.

[16] Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. Int J Radiat Oncol Biol Phys 1992;22:887–96.

[17] Gyenes G, Rutqvist LE, Liedberg A, Fornander T. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. Radiother Oncol 1998;48:185–90.

[18] Darby S, McGale P, Peto R, Granath F, Hall P, Ekbom A. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women. BMJ 2003;326:256–7.

[19] Hojris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. Lancet 1999;354:1425–30.

[20] Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN. Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 2005;97:419–24.

[21] Pedersen AN, Korreman S, Nystrom H, Specht L. Breathing adapted radiotherapy of breast cancer: reduction of cardiac and pulmonary doses using voluntary inspiration breath-hold. Radiother Oncol 2004;72:53–60.

[22] Gagliardi G, Bjohle J, Lax I, Ottolenghi A, Eriksson F, Liedberg A, et al. Radiation pneumonitis after breast cancer irradiation: analysis of the complication probability using the relative seriality model. Int J Radiat Oncol Biol Phys 2000;46:373–81.

[23] Hardman PD, Tweeddale PM, Kerr GR, Anderson ED, Rodger A. The effect of pulmonary function of local and loco-regional irradiation for breast cancer. Radiother Oncol 1994;30:33–42.

[24] Lind PA, Gagliardi G, Wennberg B, Fornander T. A descriptive study of pulmonary complications after postoperative radiation therapy in node-positive stage II breast cancer. Acta Oncol 1997;36:509–15.

[25] Lind PA, Wennberg B, Gagliardi G, Fornander T. Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. Breast Cancer Res Treat 2001;68:199–210.

[26] Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21:123–35.

[27] Gray JR, McCormick B, Cox L, Yahalom J. Primary breast irradiation in large-breasted or heavy women: analysis of cosmetic outcome. Int J Radiat Oncol Biol Phys 1991;21:347–54.

[28] Johansson S, Svensson H, Larsson LG, Denekamp J. Brachial plexopathy after postoperative radiotherapy of breast cancer patients–a long-term follow-up. Acta Oncol 2000;39:373–82.
[29] Johansson S. Late side-effects following radiotherapy after mastectomy in breast cancer patients. A long-term follow-up: Thesis, Umeå University; 2000.
[30] Travis L. Therapy-associated secondary solid cancer. Acta Oncol 2002;41:323–33.
[31] Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992;326:781–5.
[32] Turesson I, Carlsson J, Brahme A, Glimelius B, Zackrisson B, Stenerlow B. and the Swedish Cancer Society Investigation Group. Biological response to radiation therapy. Acta Oncol 2003;42:92–106.
[33] Intensity Modulated Radiation Therapy Collaborative Working Group. Intensity-modulated radiotherapy: Current status and issues of interest. Int J Radiat Oncol Biol Phys 2001; 51:880–914.
[34] Glimelius B, Isacsson U, Blomquist E, Grusell E, Jung B, Montelius A. Potential gains using high-energy protons for therapy of malignant tumours. Acta Oncol 1999;38:137–45.
[35] Lomax A. Intensity modulation methods for proton radiotherapy. Phys Med Biol 1999;44:185–205.
[36] Muren LP, Maurstad G, Hafslund R, Anker G, Dahl O. Cardiac and pulmonary doses and complication probabilities in standard and conformal tangential irradiation in conservative management of breast cancer. Radiother Oncol 2002; 62:173–83.
[37] Reed DR, Lindsley SK, Mann GN, Austin-Seymour M, Korssjoen T, Anderson BO, et al. Axillary lymph node dose with tangential breast irradiation. Int J Radiat Oncol Biol Phys 2005;61:358–64.
[38] Hurkmans CW, Borger JH, Bos LJ, van der Horst A, Pieters BR, Lebesque JV, et al. Cardiac and lung complication probabilities after breast cancer irradiation. Radiother Oncol 2000;55:145–51.
[39] Hurkmans CW, Cho BC, Damen E, Zijp L, Mijnheer BJ. Reduction of cardiac and lung complication probabilities after breast irradiation using conformal radiotherapy with or without intensity modulation. Radiother Oncol 2002;62: 163–71.
[40] Cho BC, Hurkmans CW, Damen EM, Zijp LJ, Mijnheer BJ. Intensity modulated versus non-intensity modulated radiotherapy in the treatment of the left breast and upper internal mammary lymph node chain: a comparative planning study. Radiother Oncol 2002;62:127–36.
[41] Hurkmans CW, Saarnak AE, Pieters BR, Borger JH, Bruinvis IA. An improved technique for breast cancer irradiation including the locoregional lymph nodes. Int J Radiat Oncol Biol Phys 2000;47:1421–9.
[42] Johansson J, Isacsson U, Lindman H, Montelius A, Glimelius B. Node-positive left-sided breast cancer patients after breast-conserving surgery: potential outcomes of radiotherapy modalities and techniques. Radiother Oncol 2002;65: 89–98.
[43] Lomax AJ, Cella L, Weber D, Kurtz JM, Miralbell R. Potential role of intensity-modulated photons and protons in the treatment of the breast and regional nodes. Int J Radiat Oncol Biol Phys 2003;55:785–92.
[44] Lomax A, Boehringer T, Coray A, et al. Intensity modulated proton therapy: a clinical example. Med Phys 2001;28:317–24.
[45] Severin D, Connors S, Thompson H, Rathee S, Stavrev P, Hanson J. Breast radiotherapy with inclusion of internal mammary nodes: a comparison of techniques with three-dimensional planning. Int J Radiat Oncol Biol Phys 2003;55: 633–44.
[46] Lundkvist J, Ekman M, Rehn Ericsson S, Isacsson U, Jönsson B, Glimelius B. Economic evaluation of proton radiation therapy in the treatment of breast cancer. Radiother Oncol 2005;75:179–85.
[47] Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. Eur J Cancer 1999;35:1320–5.
[48] Lievens Y, Poortmans P, Van den Bogaert W. A glance on quality assurance in EORTC study 22922 evaluating techniques for internal mammary and medial supraclavicular lymph node chain irradiation in breast cancer. Radiother Oncol 2001;60:257–65.
[49] Mansur DB, El Naqa I, Kong F, Klein EE, Taylor ME, Zoberi I, et al. Localization of internal mammary lymph nodes by CT simulation: implications for breast radiation therapy planning. Radiother Oncol 2004;73:355–7.
[50] Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215–21.
[51] Taghian AG, Assaad SI, Niemierko A, Floyd SR, Powell SN. Is a reduction in radiation lung volume and dose necessary with paclitaxel chemotherapy for node-positive breast cancer? Int J Radiat Oncol Biol Phys 2005;62:386–91.
[52] Gyenes G, Fornander T, Carlens P, Glas U, Rutqvist LE. Detection of radiation-induced myocardial damage by technetium-99m sestamibi scintigraphy. Eur J Nucl Med 1997; 24:286–92.
[53] Hardenbergh PH, Munley MT, Bentel GC, Kedem R, Borges-Neto S, Hollis D, et al. Cardiac perfusion changes in patients treated for breast cancer with radiation therapy and doxorubicin: preliminary results. Int J Radiat Oncol Biol Phys 2001;49:1023–8.