Adjuvant Radiotherapy in Breast Cancer

Rainer Souchon*

Klinik für Strahlentherapie und Radioonkologie, Allgemeines Krankenhaus Hagen gGmbH, Hagen, Germany

Key Words

Breast cancer, early · Radiotherapy, adjuvant:
postmastectomy, after breast-conserving surgery

Summary

Locoregional external beam radiation therapy using linear accelerators is an essential component of a multimodal treatment concept with a curative intent after primary surgical therapy in non-invasive and locally confined invasive breast cancer. Its important role has been confirmed at the highest level of evidence by recent results of prospective randomized clinical trials as well large meta-analyses. Whole breast irradiation following breast-conserving surgery is an integral part of breast-conserving therapy, and the indications for postmastectomy radiation therapy have been clarified. It is the decisive prognostic factor determining local and locoregional tumor control as an important therapy goal. Moreover, as an independent prognostic factor, radiotherapy positively impacts overall survival. This effect is statistically visible only after >5 years. The positive impact is directly correlated with the primary tumor stage. It is more pronounced in cases of primary nodal involvement than in node-negative disease where it is also significant.

Schlüsselwörter

Mammakarzinom, frühes · Radiotherapie, adjuvante:
nach Mastektomie, nach brusterhaltender Operation

Zusammenfassung

Die perkutane Strahlentherapie mit Photonen des Linearbeschleunigers ist wichtiger Bestandteil im kurativ ausgerichteten multimodalen Therapiekonzept nach operativer Primärbehandlung beim nicht-invasiven und beim lokal begrenzten invasiven Mammakarzinom. Ihr Stellenwert ist auf der Basis aktueller Ergebnisse prospektiver und randomisierter Studien und jüngster Metaanalysen auf hohem Evidenzniveau bestätigt worden. Die Radiotherapie ist nach brusterhaltender Operation unverzichtbar, und ihre Indikation nach Mastektomie ist präzisiert worden. Sie ist prognostisch entscheidend für die lokale und lokoregionale Tumorkontrolle als wichtigstem Therapieziel. Darüber hinaus hat sie als unabhängiger Prognosefaktor einen positiven Effekt auf das Gesamtüberleben. Dieser Effekt wirkt sich für die invasiven Karzinome statistisch erst nach >5 Jahren aus. Er korreliert positiv mit dem primären Tumorstadium. So ist er bei primärem lokoregionalen lymphonodalen Befall ausgeprägter im Vergleich zu dem bei primär vorliegendem negativen Lymphonodalstatus, jedoch auch bei dieser Konstellation signifikant.

*As member of the Breast Commission, part of the AGO (Working Group Gynecologic Oncology, German Society of Obstetrics and Gynecology)

Introduction

Over the last decades, a paradigm change has been seen in the therapy of locally confined primary breast cancer. Modern treatment concepts also consider risk-adapted aggressive locoregional therapy, in particular with regard to percutaneous radiation therapy, in order to avoid systemic relapse and its consequence – death due to breast cancer. This trend is based on large randomized clinical trials of multimodal therapy of non-invasive and locally confined invasive breast cancer. Recent meta-analyses unanimously confirm the validity of this concept [1–4]. For a long time, it remained unclear to what extent adjuvant percutaneous radiotherapy would be part of such a successful multimodal concept in various oncological situations and whether its effectiveness would be influenced by the different locoregional surgical approaches. Moreover, the question existed whether adjuvant radiotherapy substantially impacted only locoregional tumor control or also tumor-specific mortality and thus patient survival.

Published Evidence Regarding Adjuvant Radiotherapy

Regarding the impact of adjuvant percutaneous radiation therapy, recent results of completed randomized prospective clinical trials are available. These trials use state-of-the-art standard radiation techniques, take modern aspects for optimization of radiotherapy into account and do present a sufficient follow-up period [2, 3, 5–11]. A great number of these trials has been incorporated into a recent meta-analysis for adjuvant radiotherapy which comprises 78 randomized trials with 42,000 patients [2]. All studies agree on the impact of local tumor control which is strongly influenced by radiotherapy – independent of systemic therapy [2, 6, 11–13]. Adjuvant radiotherapy or its neglect do lead to significant differences in local therapy which will then substantially impact locoregional relapse rates. For example, preventing 4 local relapses will result in 1 avoided breast cancer death over the next 15 years. Or the other way around, since 1 out of 4 patients with local relapse will eventually die from the disease, preventing local relapses will lower the 15-year breast cancer mortality [2, 11]. In addition to local tumor control, adjuvant radiotherapy also positively impacts disease-free survival, 15-year breast cancer mortality and overall patient survival. Radiotherapy thus has a significant clinical relevance which has been clearly demonstrated at the highest level of evidence [LOE1]. Therefore, recent evaluations of up-to-date modern radiotherapy clearly contradict earlier meta-analyses [14, 15]. This change is mostly due to the technical advances in radiotherapy treatment over the last years. All effects are independent of patient age and are visible after mastectomy as well as after breast-conserving surgery [2, 16–22].

In order to ensure these consistently demonstrated advantages of adjuvant radiotherapy, modern radiation planning

and application techniques are necessary prerequisites. The substantial impact of optimal quality in radiation therapy planning and application, i.e. doses and clinical target volumes, on locoregional tumor control and thus on breast cancer-specific survival and cardiac mortality has been demonstrated at the highest level of evidence [2]. The necessity for adjuvant radiotherapy in patients at high risk of local/locoregional relapse is not controversial. Optimal management of patients at a suspected lower risk of local/locoregional relapse is less certain and thus being evaluated in further studies [23, 24]. These data are the foundation for recommendations and precise indications for adjuvant radiation therapy in national and international guidelines [25–29] (tables 1–2).

Techniques, Target Volumes and Radiotherapy Doses

The importance of radiation technique and its correlation with achieving a survival advantage due to local tumor control are widely accepted. Today, planning of 3-dimensional conformal irradiation of the breast and chest wall is routinely performed as an individualized standard procedure assisted by computerized tomography (or in some cases alternatively by magnetic resonance imaging) or as a virtual beam view procedure. 3-dimensional radiotherapy planning and application techniques aim at minimizing the radiation dose at the heart or other critically important organs as much as possible.

The clinical target volume for irradiation after breast-conserving surgery has to encompass the entire breast and chest wall with a small portion of the underlying lung, if indicated because of the previous tumor localization. After mastectomy, similar portals for irradiation of the thoracic wall are needed. The dose will be administered by use of tangential photon field techniques as regularly applied for treating the whole breast. Utilization of modern equipment with mega-voltage external beam radiotherapy is current standard for delivering the needed radiation dose in clinical target volumes. A total dose in a range of 45–50.0 or 50.4 Gy, respectively is considered to be adequate treatment and should be given to the whole breast and chest wall in conventional fractions, i.e. in 1.8- to 2.0-Gy daily fractions for 5 days a week (25×2 Gy or 28×1.8 Gy). In general, radiation is performed by use of high-energy photon beams of a linear accelerator. In most cases, energies of 4–6 MV will be optimal to treat the breast. An additional boost irradiation confined to the former primary tumor site, mostly achieved by use of electrons or interstitial brachytherapy techniques, is able to decrease the local relapse rate even further. In particular, premenopausal women and patients at high risk of local relapse do benefit from a boost [5, 30].

Postmastectomy Radiotherapy

Early meta-analyses analyzed studies which – due to limitations in imaging and other technical aspects – had used irradi-

Table 1. Recommendations for postmastectomy radiation therapy by the German AGO Breast Commission

Parameter	Levels of evidence ^a	Oxford grade of recommendation ^a	AGO grade of recommendation
< 3 involved lymph nodes	1a	A	++
T4 stage	1a	A	++
T3 stage	1a	A	++
R0 – resection not possible	1a	A	++
1–3 lymph nodes involved	3b	C	+/-
Age < 50 years	2b	B	+
After PST ^b : indications according to stage of disease prior to PST: cN+, cT3/T4a–d	2b	B	++

^aOxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation (http://cebm.net/levels_evidence.asp). ^bPST = Primary systemic therapy.

Table 2. Recommendations for radiation therapy of the remaining breast after breast-conserving surgery by the German AGO Breast Commission

Parameter	Levels of evidence ^a	Oxford grade of recommendation ^a	AGO grade of recommendation
Whole breast irradiation	1a	A	++
Partial breast irradiation	3	C	+/-
Boost irradiation	2a	B	+
age < 50 years	1b	A	++
node-negative, endocrine responsive, complete resection	3a	C	+/-

^aOxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation (http://cebm.net/levels_evidence.asp).

ation techniques that would be considered obsolete by today's standards [1, 2, 14, 15, 31, 32]. More modern meta-analyses have been published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 1995, 2000 and 2005 [1, 2, 32]. Using longer follow-up times, re-analyses of the 1995 data were published in 2000 [33, 34], and most recently in 2006 of the 2000 data [3].

The indication for adjuvant postmastectomy radiotherapy of the chest wall depends on certain tumor constellations. Internationally, there is consensus for adjuvant therapy in cases of pT3 or pT4 tumors, insufficient local resection (R1/R2) or extensive locoregional lymph node involvement [6, 28, 29, 35–38]. Patients who receive primary systemic therapy because of locally advanced T3 and T4 tumors before mastectomy do benefit from adjuvant radiotherapy [39, 40] (table 1). For further indication criteria, such as age, vessel invasion, low number of locoregional lymph node metastases and certain histological criteria (e.g. extensive intraductal component, extracapsular lymph node involvement), prospective clinical trials are still lacking [22]. If these criteria are present, patients do seem to benefit from adjuvant postmastectomy radiotherapy – yet, the level of evidence is rather low [38]. This also holds true for a combination of several of these parameters. Partition analysis may help in individualized decision making [41, 42]. In general, presence of several 'weaker' parameters strengthens the indication for adjuvant radiotherapy. Prospec-

tive clinical trials using appropriate stratification parameters are still needed for definite answers to these questions.

Radiotherapy after Breast-Conserving Surgery

First meta-analyses regarding radiotherapy after breast-conserving surgery were published in 2000. They considered 5 or rather 6 randomized trials [1, 21]. An additional meta-analysis published in 2004 comprised 15 trials [43] and is thus quite comparable to the recent EBCTCG meta-analysis [2]. Postoperative percutaneous whole breast irradiation is the best validated standard therapy reaching the highest level of evidence [2]. It is important to note that so far no subgroup of patients has been identified for whom radiotherapy can safely be omitted in a breast-conserving therapy concept. For patients under 50 years of age, an additional radiation dose boost at the tumor excision site is advantageous. Delivery of a localized boost dose increases the probability of local tumor control and lowers the local relapse rate even further [5, 30, 44]. The advantages of boost radiation are age-dependent and lower in older patients with no lymph node involvement (table 2). Radiation therapy confined to the area of the primary tumor after tumorectomy, partial breast irradiation (PBI), is currently being evaluated in clinical trials as an alternative to percutaneous homogeneous radiation therapy of the entire breast

[45]. The theoretical basis for this concept is the observation that most local relapses occur in the area of the primary tumor, i.e. within 1–2 cm around the site of surgery. Different techniques are being evaluated for PBI. For example, radiation of the surgical site is being performed intraoperatively using a linear accelerator or an X-ray source (IntraBeam® System, Carl Zeiss, Oberkochen, Germany). An alternative technique uses an intraoperatively implanted balloon catheter (MammoSite® RTS, Cytac Surgical Products II, Atlanta, GA, USA) which can later be loaded with the radiation source as an afterloading approach.

A major disadvantage of the intraoperative approaches is the fact that the indication needs to be decided intraoperatively. If postoperative definitive histology does not show adequate resection margins and renewed resection becomes necessary, the situation will become complicated. Furthermore, dose distributions might not be favorable using these new methods: Either the surgical site is irradiated from only one side using an intraoperative linear accelerator, or a very steep dose decrease results in extreme dose inhomogeneities (IntraBeam or MammoSite systems). Postoperative interstitial high dose rate brachytherapy avoids these disadvantages. Using this approach, reloadable catheters are implanted into the surgical site postoperatively, approximately 3–6 weeks after surgery, i.e. at the usual time for start of postoperative radiation therapy. Irradiation is then performed as an afterloading procedure. A dose of 20 Gy is applied within approximately 4 days. Advantages of this technique compared to other techniques are a correct indication, i.e. selection of patients based on postoperative definitive histology, and better dose distribution. This approach is currently being evaluated in 3 trials in the USA and Europe [13, 29].

Various trials regarding PBI, a seemingly very attractive experimental alternative radio-oncological treatment concept, are currently being performed. Criteria for assessment of individual risk and eligibility for this therapy concept have not yet been unequivocally defined. Only very scarce phase III data are so far available for assessment of long-term outcome. Thus, definite conclusions about this therapy option with regard to it being a potential comparable alternative to whole breast irradiation are not possible at this point. PBI should thus not be performed outside of clinical trials [13, 29].

Radiotherapy of the Axilla or Other Regional Lymphatics

For breast cancer patients, ipsilateral lymph edema of the arm as well as impairment of shoulder mobility or brachial plexus are rather relevant therapy sequelae. They may severely lower patients' quality of life. Thus, specific morbidities attributable to surgery or radiotherapy do impact functional outcome. Complete axillary dissection may offer the possible advantage of adequate lymph node staging, whereas potential postoperative radiotherapy may make functional impairments more severe. The concept of sentinel node biopsy takes these considerations into account. Internationally, recommendations regarding postoperative radiotherapy of the axilla or other regional lymphatics are not uniform. This is due to the fact that radiotherapeutic effects from retrospective studies are not well validated, and large international prospective trials in substantial collectives are currently still ongoing and their results are not yet available.

An indication for radiation therapy of regional lymphatics is only to be considered for selected patients [9, 11, 36, 46]. Irradiation of a previously surgically treated axilla is usually not indicated due to the rather low incidence of axillary relapses (i.e. approximately 2% after adequate axillary dissection). Standard sentinel lymph node procedure is considered to be an equal option, and indications for adjuvant radiotherapy are thus similar to those in the case of adequate axillary dissection. Irradiation of the axillary apex and supraclavicular lymph nodes is indicated if tumor involvement is present in more than 3 axillary nodes, since this situation is associated with a substantial (> 5%) risk of further tumor involvement in these additional lymph node areas. Irradiation of the internal mammary lymphatics is currently being evaluated in a large EORTC trial. The rationale for this trial is based on retrospective data suggesting a 5% 5-year survival improvement due to irradiation of ipsilateral internal mammary lymph nodes in patients with primary tumors in the medial quadrants or central location and involvement of more than 3 axillary lymph nodes. Yet, irradiation of internal mammary lymph nodes may cause a significant burden on the heart or lungs. Thus, stringent indications for internal mammary lymph node radiotherapy have not yet been defined.

References

- 1 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.
- 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 randomised trials. *Lancet* 2005;366:2087–2106.
- 3 Gebski V, Lagleva M, Keech A, et al.: Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. *J Natl Cancer Inst* 2006;98:26–38.
- 4 Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N: Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project Node-Positive Adjuvant Breast Cancer Trials. *J Clin Oncol* 2006;24:2028–37.
- 5 Bartelink H, Horiot JC, Poortmans P, Struikmans H, van den Bogaert W, Barillot I, Fourquet A, Borger J, Jager J, Hoogenraad W, Collette L, Pierart M, European Organization for Research and Treatment of Cancer Radiotherapy and Breast Cancer Groups: Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;345: 1378–87.

- 6 Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J: Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006;24:2268–75.
- 7 Pierce LJ: The use of radiotherapy after mastectomy: a review of the literature. *J Clin Oncol* 2005;23:1706–17.
- 8 Prosnitz LR, Marks LB: Postmastectomy radiotherapy: quality counts! *J Natl Cancer Inst* 2006;98:3–4.
- 9 Taghian A, Jeong JH, Mamounas E, et al.: Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol* 2004;22:4247–54.
- 10 Truong PT, Olivetto IA, Whelan TJ, Levine M, Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer: Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy. *CMAJ* 2004;170:1263–73.
- 11 Whelan T, Levine M: More evidence that locoregional radiation therapy improves survival: what should we do? *J Natl Cancer Inst* 2005;97:82–4.
- 12 Fisher B, Bryant J, Dignam JJ, 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;20:4141–9.
- 13 Van der Hage JA; Putter H, Bonnema J, et al.: Impact of locoregional treatment on the early-stage breast cancer patients: a retrospective analysis. *Eur J Cancer* 2003;39:2192–9.
- 14 Cuzick J, Stewart H, Peto R, et al.: Overview of randomized trials comparing radical mastectomy without radiotherapy against simple mastectomy with radiotherapy in breast cancer. *Cancer Treat Rep* 1987;71:7–14.
- 15 Cuzick J, Stewart H, Rutqvist L, et al.: Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994;12:447–53.
- 16 Fisher B, Anderson S, Bryant J, et al.: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233–41.
- 17 Lee JC, Truong PT, Kader HA, Speers CH, Olivetto IA: Postmastectomy radiotherapy reduces locoregional recurrence in elderly women with high-risk breast cancer. *Clin Oncol (R Coll Radiol)* 2005;17:623–9.
- 18 Olivetto IA, Truong PT, Chua B: Postmastectomy radiation therapy: who needs it? *J Clin Oncol* 2004;22:4237–9.
- 19 Truong PT, Lee J, Kader HA, Speers CH, Olivetto IA: Locoregional recurrence risks in elderly breast cancer patients treated with mastectomy without adjuvant radiotherapy. *Eur J Cancer* 2005;41:1267–77.
- 20 Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, Bing Oei S, Peterse HL, Pierart M, Poortmans PM, Struikmans H, van den Bogaert W, Bartelink H, EORTC Radiotherapy, Breast Cancer Groups: Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer* 2003;39:932–44.
- 21 Whelan TJ, Julian J, Wright J, et al.: Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000;18:1220–9.
- 22 Zhou P, Recht A: Young age and outcome for women with early-stage invasive breast carcinoma. *Cancer* 2004;101:1264–74.
- 23 Solin LJ: Is excision alone adequate treatment for low-risk ductal carcinoma-in-situ of the breast? *J Clin Oncol* 2006;24:1017–9.
- 24 Wong JS, Kaelin CM, Troyan SL, Gadd MA, Gelman R, Lester SC, Schnitt SJ, Sgroi DC, Silver BJ, Harris JR, Smith BL: Prospective study of wide excision alone for ductal carcinoma in situ of the breast. *J Clin Oncol* 2006;24:1031–6.
- 25 German Cancer Society and AWMF (DE), Association of Scientific Medical Societies: Quality Assurance in Oncology. Interdisciplinary S3 Guidelines for the Diagnosis and Treatment of Breast Cancer in Women. www.g-i-n.net/download/files/S3_Diagn_Ther_engl.pdf.
- 26 Kurtz J: Position paper: EUSOMA guidelines. The curative role of adjuvant radiotherapy in the treatment of operable breast cancer. *Eur J Cancer* 2002;38:19618–74.
- 27 National Cancer Institute (NCI USA): Breast Cancer, 2004. www.meb.uni-bonn.de/cancer.gov/CDR0000062787.html.
- 28 Recht A, Edge SB, Solin LJ, et al., for the American Society of Clinical Oncology: Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1539–69.
- 29 Sauer R, Budach W, Dunst J, Feyer P, Haase W, Harms W, Sautter-Bihl ML, Souchon R, Wenz R: Leitlinien in der Radioonkologie: Radiotherapie des Mammakarzinom – Version 2005. *Strahlenther Onkol* 2006;182(suppl 1):1–28.
- 30 Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, Mamelle N, Gerard JP: 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;15:963–8.
- 31 Early Breast Cancer Trialists' Collaborative Group: Treatment of Early Breast Cancer. *Worldwide Evidence 1985–1990*, vol 1. Oxford, Oxford University Press, 1990.
- 32 Early Breast Cancer Trialists' Collaborative Group: Effects of radiotherapy and surgery in early breast cancer: an overview of the randomised trials. *N Engl J Med* 1995;333:1444–55.
- 33 Van de Steene J, Soete G, Storme G: Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. *Radiother Oncol* 2000;55:263–72.
- 34 Van de Steene J, Vinh-Hung V, Cutuli B, Storme G: Adjuvant radiotherapy for breast cancer: effects of longer follow-up. *Radiother Oncol* 2004;72:35–43.
- 35 Harris JR, Halpin-Murphy P, McNeese M, et al.: Consensus statement on postmastectomy radiation therapy. *Int J Radiat Oncol Biol Phys* 1999;44:989–90.
- 36 Ragaz J, Olivetto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, Knowling MA, Coppin CM, Weir L, Gelmon K, Le N, Durand R, Coldman AJ, Manji M: Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005;97:116–26.
- 37 Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, van Tienhoven G, Andersen KW, Sylvester RJ, van Dongen JA, Danish Breast Cancer Cooperative Group, Breast Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer: Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001;19:1688–97.
- 38 Voordeckers M, van de Steene J, Vinh-Hung V, Storme G: Adjuvant radiotherapy after mastectomy for pT1-pT2 node negative (pN0) breast cancer: is it worth the effort? *Radiother Oncol* 2003;68:227–31.
- 39 Garg AK, Strom EA, Mc Neese MD, Buzdar AU, Hortobagyi GN, Kuerer HM, Perkins GH, Singletary SE, Hunt KK, Sahin A, Schechter N, Valero V, Tucker SL, Buchholz TA: T3 disease at presentation or pathological involvement of four or more lymph nodes predict for locoregional recurrence in stage II breast cancer treated with neoadjuvant chemotherapy and mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;59:138–45.
- 40 Huang EH, Tucker SL, Strom EA, 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;22:4691–99.
- 41 Katz A, Buchholz TA, Thames H, et al.: Recursive partitioning analysis of locoregional recurrence patterns following mastectomy: implications for adjuvant irradiation. *Int J Radiat Oncol Biol Phys* 2001;50:397–403.
- 42 Katz A, Strom EA, Buchholz TA, et al.: The influence of pathologic tumor characteristics on locoregional recurrence rates following mastectomy. *Int J Radiat Oncol Biol Phys* 2001;50:735–42.
- 43 Vinh-Hung V, Verschraegen C: Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst* 2004;96:115–21.
- 44 Poortmans P, Bartelink H, Horiot JC, Struikmans H, van den Bogaert W, Fourquet A, Jager J, Hoogenraad W, Rodrigus P, Warlam-Rodenhuis C, Collette L, Pierart M, EORTC Radiotherapy and Breast Cancer Groups: The influence of the boost technique on local control in breast conserving treatment in the EORTC 'boost versus no boost' randomised trial. *Radiother Oncol* 2004;72:25–33.
- 45 Arthur DW, Vicini FA: Accelerated partial breast irradiation as part of breast conservation therapy. *J Clin Oncol* 2005;23:1726–35.
- 46 Truong PT, Olivetto IA, Kadar HA, Panades M, Speers CH, Barthelet E: Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;61:1337–47.