ORIGINAL ARTICLE: LIMITED-RESOURCE INTERVENTIONS

Radiotherapy for Breast Cancer in Countries with Limited Resources: Program Implementation and Evidence-Based Recommendations

Nuran Senel Bese, MD,* Krystyna Kiel, MD,† Brahim El-Khalil El-Gueddari, MD,‡ Oladapo Babatunde Campbell, MD,§ Baffour Awuah, MD,¶ and Bhadrasain Vikram, MD,# for the International Atomic Energy Agency

**Cerrahpasa Medical School, Istanbul, Turkey; †Northwestern University, Chicago; ‡Institut National d'Oncologie, Rabat, Morocco; §University College Hospital, Ibadan, Nigeria; ¶Komfo Anokye Teaching Hospital, Kumasi, Ghana; and #International Atomic Energy Agency of the United Nations, Vienna, Austria*

■ **Abstract:** Radiotherapy is an essential part of the multimodality treatment of breast cancer. Applying safe and effective treatment requires appropriate facilities, staff, and equipment, as well as support systems, initiation of treatment without undue delay, geographic accessibility, and completion of radiotherapy without undue prolongation of the overall treatment time. Radiotherapy can be delivered with a cobalt-60 unit or a linear accelerator (linac). In early stage breast cancer, radiotherapy is an integral part of breast-conserving treatment. Standard treatment includes irradiation of the entire breast for several weeks, followed by a boost to the tumor bed in women age 50 years or younger or those with close surgical margins. Mastectomy is an appropriate treatment for many patients. Postmastectomy irradiation with proper techniques substantially decreases local recurrences and improves survival in patients with positive axillary lymph nodes. It is also considered for patients with negative nodes if they have multiple adverse features such as a primary tumor larger than 2 cm, unsatisfactory surgical margins, and lymphovascular invasion. Many patients present with locally advanced or inoperable breast cancer. Their initial treatment is by systemic therapy; after responding to systemic therapy, most will require a modified radical mastectomy followed by radiotherapy. For those patients in whom mastectomy is still not possible after initial systemic therapy, breast and regional irradiation is given, followed whenever possible by mastectomy. For patients with distant metastases, irradiation may provide relief of symptoms such as pain, bleeding, ulceration, and lymphedema. A single fraction of irradiation can effectively relieve pain from bone metastases. Radiotherapy is also effective in the palliation of symptoms secondary to metastases in the brain, lungs, and other sites. Radiotherapy is important in the treatment of women with breast cancer of all stages. In developing countries, it is required for almost all women with the disease and should therefore be available. ■

Key Words: breast cancer, developing countries, health resources, radiation oncology, radiation therapy, radiotherapy

Radiotherapy is an essential component of the treatment of breast cancer. Depending on the stage of disease, this therapy can reduce the risk of local recurrence, improve survival, and provide palliation of symptoms. Available data suggest that the incidence of breast cancer is increasing in countries with limited resources (1), which typically have restricted or no access to radiotherapy (2–5). Therefore, implementing and expanding radiotherapy programs will be imperative to ensure the best possible outcomes for women with the disease.

Address correspondence and reprint requests to: Bhadrasain Vikram, MD, Head, Section of Applied Radiation Biology and Radiotherapy, International Atomic Energy Agency, P.O. Box 100, Wagramer Strasse 5, A-1400 Vienna, Austria, or e-mail: b.vikram@iaea.org.

The Breast Journal, Volume 12 Suppl. 1, 2006 S96–S102

In this article we review the resource requirements for implementing a radiotherapy program in the limited-resource setting, with special reference to treating breast cancer, and we discuss possible strategies for overcoming barriers to a radiotherapy program. In addition, we provide evidence-based recommendations for radiotherapy for breast cancer in such settings.

REQUIREMENTS FOR SAFE AND EFFECTIVE RADIOTHERAPY FOR BREAST CANCER

In delivering radiotherapy for breast cancer, as for other cancers, a health care system must strive to meet at least basic staff and equipment requirements, each of which plays a role in ensuring that the therapy is both safe and effective (Table 1) (6). A major thrust of the program in human health of the International Atomic Energy

Table 1. Roles of Staff and Equipment Requirements in Safe and Effective Radiotherapy for Breast Cancer (6)

Requirement	Role(s)
Staff	
Radiation oncologist	Clinical evaluation, therapeutic decision, target volume localization, treatment planning, simulation/verification of treatment plan, treatment evaluation during treatment, follow-up examinations
Medical physicist	Quality control, computerized treatment planning, complex calculations and quality checks
RTT	Simulation/verification of treatment plan, routine calculations and quality checks, treatment
Maintenance technician[a]	Maintenance of equipment
Equipment	
Megavoltage teletherapy unit[b]	Radiation source
Dosimetry equipment	Physical quality assurance
Clinical QA equipment[c]	Clinical quality assurance
Immobilization devices	Accuracy of therapy
Shielding devices	Protection of healthy tissues such as heart, lungs, and spinal cord
Treatment planning computer system	Calculation of radiation distribution

[a]Required if a linear accelerator (linac) is being used.
[b]A cobalt-60 unit or linac; choice will depend on the factors discussed in the text. Breast brachytherapy is investigational at this time.
[c]Includes a simulator (fluoroscopic or computed tomography).
QA, quality assurance; RTT, radiotherapy technologist/radiographer.

Agency (IAEA) is addressing the need for radiotherapy in countries with limited resources (7). The IAEA has a long track record of providing essential equipment and training staff to safely treat patients with cancer. It has delivered more than $57 million in radiotherapy technology to developing member states since 1981 through the Technical Cooperation program, under which assistance is provided to such states for establishing or upgrading facilities for cancer treatment.

Lack of well-trained staff results in underuse or inappropriate use of even the existing scarce radiotherapy facilities in many countries. Therefore the IAEA provides initial education and training as well as continuing professional development activities for professionals in radiation oncology and allied fields (e.g., physicians, technicians, nurses, maintenance engineers). Another reason for the suboptimal use of existing facilities is the lack of a quality culture in many institutions in developing countries. Many IAEA activities therefore focus on establishing and strengthening quality assurance programs.

The central equipment requirement for radiotherapy for breast cancer is a megavoltage teletherapy unit, either a cobalt-60 unit or a linear accelerator (linac). At present, although the developing world has as many patients with breast cancer as the developed world, it has only about half as many radiotherapy units, with dozens of countries having no radiotherapy at all (8). Either a cobalt unit or a linac can be used for radiotherapy for breast cancer, but experience in countries with limited resources has shown that the downtime of linacs is generally considerably greater. Any interruption to treatment due to equipment breakdown adversely affects patients' outcomes. The longer or more frequent the interruptions, the worse the impact. There have been numerous instances where, even after an institution acquired a linac, few patients could be treated because the proper support arrangements were not made. There are many technical differences between cobalt units and linacs, including the build-up region, penumbra, depth dose, dose rate, versatility, beam profile, ease of maintenance, and decommissioning. These are discussed in detail elsewhere (6,9,10). In addition to the teletherapy equipment, high-quality treatment by radiotherapy requires certain quality assurance tools such as an imaging device (a fluoroscopic or computed tomography simulator), immobilization devices, shielding devices, a treatment planning computer system, and tools for dosimetry.

Delivery of safe and effective radiotherapy also requires addressing certain logistical issues. Specifically, in addition to the staff and equipment requirements, the health care system must be able to provide the physical facility for radiotherapy, support systems that allow delivery of therapy over a period of weeks, initiation of treatment without long delay, and geographic accessibility to patients.

Although the initial investment in establishing radiotherapy is significant, the long life of radiotherapy equipment (20–30 years) means that the cost per patient treated can be surprisingly modest in an efficiently run facility. Nonetheless, given that substantial initial investment, and in light of the competing needs in countries with limited resources, collaborative and innovative approaches are called for. For example, technical cooperation programs between nations, or with international organizations such as the IAEA (11), can aid in the establishment of radiotherapy in countries with limited resources. Advances in telecommunications may also enable cost-effective approaches by linking radiotherapy facilities with

differing levels of treatment capability and expertise by digital networks or satellite (12). Continued exploration of such strategies will be essential to meet the goal of delivering radiotherapy to all women with breast cancer who need it in limited-resource countries.

RECOMMENDATIONS FOR RADIOTHERAPY FOR BREAST CANCER

Radiotherapy has an important role in the treatment of breast cancer at every stage. In early stage disease, radiotherapy is an integral part of breast-conserving therapy. For patients with more advanced cancers, adjuvant radiotherapy substantially decreases the risk of local recurrence, and also improves the survival among patients with positive axillary lymph nodes (13–16). In locally advanced disease (often the most common presentation in the limited-resource setting), after neoadjuvant systemic therapy, patients require both radiotherapy and modified radical mastectomy in an effort to achieve local control. In addition, radiotherapy is a valuable tool for the palliation of distant metastasis such as bone and brain metastases, as well as palliation for local recurrences.

Delivery of radiotherapy for breast cancer in the doses needed and according to the schedules supported by current evidence (discussed subsequently and summarized in Table 2) is essential for its effectiveness, as well as its safety. Ongoing studies are exploring the possibility of using lower doses or shorter schedules, which would reduce costs and workloads, but their use should be considered investigational at this time.

Breast cancer requires multimodality treatment that, in addition to radiotherapy, includes surgery and systemic therapy (chemotherapy, hormonal therapy, or both). Approaches for integrating these therapies for safe and effective breast cancer treatment in the limited-resource setting are given in an accompanying guideline (17). Here we elaborate on delivery of radiotherapy in such settings by discussing the evidence base, doses and schedules, and issues such as sequencing with other therapies.

Whole-Breast Radiotherapy

Early stage (stage I or II) breast cancer is surgically treated by either excision of the cancer (lumpectomy) with negative margins or a mastectomy. Disease in the axilla is assessed by either axillary dissection or a sentinel node biopsy followed by axillary dissection if the sentinel node is positive. Radiotherapy is delivered to the breast in the case of breast-conserving surgery, or is delivered to the chest wall after mastectomy if axillary lymph nodes are

Table 2. Recommended Doses and Schedules for Radiotherapy for Breast Cancer

Stage I or II breast cancer	Locally advanced breast cancer	Metastatic or recurrent breast cancer
Whole-breast radiotherapy All patients: 50 Gy in 25 fractions over 5 weeks or 42.5 Gy in 16 fractions over 22 days, administered five times per week Patients ≤50 years of age and patients with close surgical margins: an additional 16 Gy boost to the tumor bed Postmastectomy radiotherapy Patients with positive axillary lymph nodes: 50 Gy in 25 fractions over 5 weeks, administered five times per week to the chest wall and supraclavicular area; the axilla is included only if axillary dissection was inadequate Patients with negative axillary lymph nodes who have multiple adverse features (e.g., primary tumor larger than 2 cm, unsatisfactory surgical margins, lymphovascular invasion): 50 Gy in 25 fractions over 5 weeks, administered five times per week to the chest wall	Patients who have a response to systemic therapy and can undergo breast-conserving surgery: whole-breast radiotherapy Patients who have a response to systemic therapy and require radical or modified radical mastectomy: postmastectomy radiotherapy Patients whose tumors remain unresectable after two regimens of non-cross-resistant chemotherapy: whole-breast radiotherapy (including regional lymph nodes) followed, if possible, by mastectomy; if mastectomy is still not possible, then a further boost to the gross tumor using shrinking fields	Patients with single symptomatic bone metastases: local-field radiotherapy with a single 8 Gy fraction Patients with multiple symptomatic bone metastases: wide-field (e.g., hemibody) radiotherapy with 12 Gy in four fractions over 2 days, or—if preceded by intravenous ondansetron and dexamethasone—6–8 Gy in a single fraction Patients with symptomatic brain metastases: steroids and whole-brain radiotherapy (30 Gy in 10 fractions or 20 Gy in 5 fractions); highly selected patients may benefit from craniotomy or radiosurgery Patients with symptomatic soft tissue metastases: irradiation of the metastases Patients with locally recurrent breast cancer after mastectomy: irradiation of the chest wall and regional lymph nodes, with a further boost to the gross tumor using shrinking fields

involved or certain other adverse features are present (discussed in a later section).

Randomized trials have shown that there are no significant differences in disease-free or overall survival between patients treated by mastectomy and those treated by breast-conserving surgery and whole-breast radiotherapy (18–21). The main benefit of breast-conserving surgery and radiotherapy is preservation of body image and a better quality of life. Randomized studies evaluating the use of breast-conserving surgery plus adjuvant systemic treatment have demonstrated higher rates of local recurrence than after breast-conserving surgery plus radiotherapy and adjuvant systemic treatment, but major differences in survival have not been observed (22,23). In view of the higher rates of local recurrence, breast irradiation is currently recommended for most patients who undergo breast-conserving surgery. Breast-conserving surgery requires 1) high-quality breast imaging (mammography and ultrasound) and pathology services to ensure tumor-free margins of excision, 2) surgeons experienced in achieving a good cosmetic result with negative pathologic margins of excision, and 3) radiotherapy facilities.

Radiotherapy should be started without a long delay after breast-conserving surgery because a prolonged postoperative interval may compromise local control (24,25). When chemotherapy is indicated, radiotherapy may follow chemotherapy, but for patients with close surgical margins, radiotherapy can be given first. In a prospective randomized trial, there were no significant differences in time to any event, distant metastasis, or death, whether radiotherapy or chemotherapy was given first (26). Concomitant chemoradiotherapy can reduce the overall treatment time, but the concomitant administration of anthracyclines should be avoided because of the risk of increased skin and cardiac morbidity (27). Regimens such as cyclophosphamide, methotrexate, fluorouracil (CMF) are cost effective and can be given concomitantly with irradiation (28,29). Radiation therapy should be completed without undue prolongation of the overall treatment time (30).

Most local relapses are observed in the vicinity of the primary tumor bed, and for this reason, partial breast irradiation is currently under investigation. The target volume is smaller; therefore the radiation can be accelerated and completed in only 1 week. However, robust long-term results and toxicity evaluations are not yet available. At present, after breast-conserving surgery, the target volume for irradiation should include the whole breast.

The most common schedule for irradiation used in clinical practice is 50 Gy in 25 fractions to the whole breast, administered daily, five times per week. In a large randomized trial, however, a shorter fractionation schedule (42.5 Gy in 16 fractions over 22 days) proved to be just as safe and effective (31). Other schedules (e.g., 40 Gy in 3 weeks) are currently under investigation (32). The shorter schedules permit more efficient use of resources, and thus more women can be treated with the existing equipment and personnel in countries with limited resources.

Evidence suggests that boost radiation to the lumpectomy site significantly improves the local control rate for women 50 years of age or younger (33). Therefore a 16 Gy additional radiation dose to the tumor bed is recommended for younger women, as well as for women with close surgical margins. The boost dose can be delivered by photons, electrons, or brachytherapy (34).

Postmastectomy Radiotherapy

Early Stage Breast Cancer Total mastectomy remains an appropriate treatment for many patients with breast cancer in the developing world. Radiotherapy following mastectomy substantially improves local control (35,36). Local recurrence after mastectomy usually occurs within the first 12–24 months, even after adjuvant systemic therapy, most commonly in the chest wall, followed by the supraclavicular fossa. The major risk factor is positive axillary lymph nodes (37). Other risk factors are large tumor size, positive margins of resection, and lymphovascular invasion (38).

Studies have demonstrated that the use of postmastectomy irradiation improves overall survival in women with axillary lymph node-positive breast cancer (13–16). Postoperative radiotherapy to the chest wall and supraclavicular area is therefore recommended for all patients with four or more positive lymph nodes and should be considered for patients with one to three positive lymph nodes. Axillary irradiation is given only to those patients who did not undergo an adequate axillary dissection. Irradiation of the axilla is, in general, not recommended (37,39). The axillary and internal mammary regions are relatively uncommon sites of local recurrence (in comparison with the chest wall), while the morbidity from axillary irradiation (e.g., arm edema) or internal mammary irradiation (e.g., cardiac toxicity) is of concern (40,41). If sophisticated techniques of modern treatment planning and delivery are available, internal mammary irradiation is recommended for patients with clinically or pathologically positive internal mammary lymph nodes, and is considered for patients if the primary tumor is located at the inner quadrant with the other adverse risk factors. On the basis of a recent retrospective review, postoperative chest wall irradiation should also

considered for patients with negative axillary lymph nodes who have multiple adverse features (e.g., a primary tumor larger than 2 cm, unsatisfactory surgical margins, or lymphovascular invasion) (38).

A regimen of 50 Gy in 5 weeks is widely used for postoperative irradiation, but more rapid fractionation regimens (e.g., 40 Gy in 3 weeks) are under investigation in randomized trials, some already completed (32,42). Such approaches, with appropriate quality control, may be particularly beneficial in countries with limited resources by reducing the radiotherapy workload and costs.

Information on the impact of the sequencing of postmastectomy radiotherapy and systemic chemotherapy on survival is limited. At present, radiotherapy is most commonly delivered after the completion of chemotherapy in patients with node-positive disease.

Locally Advanced Breast Cancer In developing countries, a considerable proportion of the patients present with locally advanced breast cancer (LABC) that is inoperable due to direct extension to the ribs, intercostal muscles, or skin; edema (including peau d'orange) or ulceration of the skin of the breast; satellite skin nodules confined to the same breast; inflammatory carcinoma; metastases to the ipsilateral internal mammary lymph nodes; or metastases to the ipsilateral supraclavicular lymph nodes. Patients with LABC have a high probability of distant metastasis as well as a high probability of local recurrence. Initial treatment of LABC is systemic therapy. Approximately 80% of inoperable tumors treated with chemotherapy may regress sufficiently to become operable (43,44). Neoadjuvant hormonal therapy is beneficial in patients with hormone receptor-positive tumors (45). Following systemic therapy, most patients require a radical or modified radical mastectomy, followed by radiotherapy (selected noninflammatory breast cancers exhibiting a complete or partial clinical response to initial chemotherapy can be considered for breast-conserving surgery followed by radiotherapy). Unresectable tumors that remain unresectable even after two regimens of non–cross-resistant chemotherapy should be irradiated. This should be followed, whenever feasible, by mastectomy. If mastectomy is still not possible, then definitive radiotherapy can be applied, with a further boost to the gross tumor using shrinking fields.

Palliative Radiotherapy

In patients with metastatic breast cancer, radiotherapy is an effective tool for palliation of the symptoms. The goal is to prevent or relieve symptoms or loss of function for as long as possible. Patients with bone metastases comprise the largest group receiving palliative radiotherapy. Radiotherapy can prevent pathologic fractures in patients with lytic lesions in weight-bearing bones. Traditionally local-field radiotherapy has been used for patients with symptomatic bone metastases. Evidence suggests that significant symptomatic relief can be obtained with a single 8 Gy fraction, a very cost-effective strategy (46–49). Wide-field radiotherapy (e.g., hemibody irradiation) can be used for patients with multiple bone metastases. The IAEA conducted a multinational, prospective, randomized trial that showed that hemibody radiation of 12 Gy in four fractions delivered over 2 days was a suitable treatment regimen (50). Others have suggested that hemibody irradiation of 6–8 Gy in a single dose is also safe and effective, if preceded by intravenous ondansetron and dexamethasone (51).

Patients with brain metastases can survive for many months after radiotherapy. Whole-brain irradiation and steroids are recommended for alleviating symptoms from brain metastases. Selected patients with no extracranial disease who have one or few metastases and a good performance status can be treated with craniotomy or radiosurgery if available (52).

Palliative radiotherapy is also useful for patients with soft tissue metastases causing pain, discharge, or bleeding.

Locally recurrent breast cancer after mastectomy can occasionally be cured with radiotherapy to the chest wall and regional nodes. The likelihood of tumor control increases with a longer disease-free duration since the initial therapy and resection of the recurrent disease, and also depends on the number of sites involved.

CONCLUSION

Delivery of safe and effective radiotherapy for breast cancer requires a substantial investment of resources. However, this therapy is important in the treatment of women with breast cancer of all stages. With appropriate treatment, many women are cured of breast cancer, while many others live longer with the disease and have a better quality of life. Use of evidence-based doses and techniques is essential for ensuring the best possible clinical outcomes and avoiding complications. In developing countries, radiotherapy is required for almost all women with breast cancer and should therefore be available.

REFERENCES

1. Parkin DM, Fernandez LMG. Use of statistics to assess the global burden of breast cancer. *Breast J* 2006;12(suppl. 1);S70–80.

2. Levin CV, El Gueddari B, Meghzifene A. Radiation therapy in Africa: distribution and equipment. *Radiother Oncol* 1999;52:79–84.

3. Tatsuzaki H, Levin CV. Quantitative status of resources for radiation therapy in Asia and Pacific region. *Radiother Oncol* 2001;60:81–89.

4. Zubizarreta EH, Poitevin A, Levin CV. Overview of radiotherapy resources in Latin America: a survey by the International Atomic Energy Agency (IAEA). *Radiother Oncol* 2004;73:97–100.

5. Levin V, Tatsuzaki H. Radiotherapy services in countries in transition: gross national income per capita as a significant factor. *Radiother Oncol* 2002;63:147–50.

6. International Atomic Energy Agency. *Design and Implementation of a Radiotherapy Programme: Clinical, Medical Physics, Radiation Protection and Safety Aspects*. IAEA TECDOC-1040. Vienna, Austria: IAEA, 2005.

7. International Atomic Energy Agency. Fighting cancer through radiotherapy. IAEA maps out programme of action for cancer therapy. Available at http://www.iaea.org/NewsCenter/Features/Radiotherapy/index.shtml; accessed July 5, 2005.

8. Stewart BW, Kleihues P, eds. *World Cancer Report*. Lyon, France: World Health Organization, 2003.

9. Reddy KS. Choice of a teletherapy unit. In: Agarwal SP, Rao YN, Gupta S, eds. *Fifty Years of Cancer Control in India*. New Delhi, India: National Cancer Control Programme, 2002. Available at http://mohfw.nic.in/healthprogmain.html; accessed July 5, 2005.

10. Deore SM, Saple MP, Pandhi R, Dinshaw KA. Treatment planning for irradiation of breast cancer—comparative study of physical aspects of cobalt vs linear accelerator. *Indian J Cancer* 1985;22:167–72.

11. Director General, International Atomic Energy Agency. *Technical Cooperation Report for 2003*. Vienna, Austria: IAEA, 2004.

12. Datta RN, Rajasekar D. Improvement of radiotherapy facilities in developing countries: a three-tier system with a teleradiotherapy network. *Lancet Oncol* 2004;5:695–98.

13. Recht A, Edge SB, Solin LJ, *et al.* Post-mastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Surg Oncol* 2001;19:1539–69.

14. Steene JV, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves overall survival. *Radiother Oncol* 2000;55:263–72.

15. Early Breast Cancer Trialists' Collaborative Group. Favorable and unfavorable effects on long term survival of radiotherapy for early breast cancer. *Lancet* 2000;355:1757–70.

16. Ragaz J, Olivotto IA, Spinelli JJ, *et al.* 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.

17. Eniu A, Carlson RW, Aziz Z, *et al.* Breast cancer in limited-resource countries: treatment and allocation of resources. *Breast J* 2006;12(suppl. 1):S38–53.

18. 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.

19. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. *N Engl J Med* 1995;333:1444–55 [erratum, *N Engl J Med* 1996;334:1003].

20. van Dongen JA, Voogd AC, Fentiman IS, *et al.* Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000;19:1143–50.

21. Veronesi U, Cascinelli N, Mariani L, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–32.

22. Hughes KS, Schnaper LA, Berry D, *et al.* Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351:971–77.

23. McCready D, Fyles A, Manchul L, *et al.* Randomized trial of lumpectomy and tamoxifen with or without breast radiation for node negative patients =50 years old and subgroup analysis of T1 tumors: implications for partial breast irradiation [abstract 31]. *Breast Cancer Surg Treat* 2004;88(suppl.):S17.

24. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. *J Clin Oncol* 2003;21:555–63.

25. Recht A, Cone SE, Henderson IC, *et al.* The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. *N Engl J Med* 1996;334:1356–61.

26. Bellon JR, Come SE, Gelman RS, *et al.* Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *J Clin Oncol* 2005;23:1934–40.

27. National Institutes of Health Consensus Development Conference statement. Adjuvant therapy for breast cancer. *J Natl Cancer Inst* 2001;30(suppl. 13):5–11.

28. Markiewicz DA, Fox KR, Schultz DJ, *et al.* Concurrent chemotherapy and radiation for breast conservation treatment of early-stage breast cancer. *Cancer J Sci Am* 1998;4:185–93.

29. Dubey A, Recht A, Come SE, *et al.* Concurrent CMF and radiation therapy for early stage breast cancer: results of a pilot study. *Int J Radiat Oncol Biol Phys* 1999;45:877–84.

30. Bese NS, Sut PA, Ober A. The effect of treatment interruptions in the postoperative irradiation of breast cancer. *Oncology* 2005;69:214–23.

31. Whelan T, MacKenzie R, Julian J, *et al.* Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94:1143–50.

32. Winfield EA, Deighton A, Venables K, *et al.* Survey of tangential field planning and dose distribution in the UK: background to the introduction of the quality assurance programme for the START trial in early breast cancer. *Br J Radiol* 2003;76:254–59.

33. Vrieling C, Collette L, Fourquet A, *et al.* The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC "boost vs. no boost" trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. *Radiother Oncol* 2000;55:219–32.

34. Poortmans P, Bartelink H, Horiot JC, *et al.* 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.

35. Buzdar AU, McNeese MD, Hortobagyi GN, *et al.* Is chemotherapy effective in reducing the local failure rate in patients with operable breast cancer? *Cancer* 1990;65:394–99.

36. Tennrall-Nittby L, Tengrup J, Landberg T. The total incidence of locoregional recurrence in a randomized trial of breast cancer TNM stage II: the south Sweden Breast Cancer Trial. *Acta Oncol* 1993;32:641–46.

37. 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.

38. Jagsi R, Raad RA, Goldberg S, *et al.* Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 2005;62:1035–39.

39. Adenipekun A, Campbell OB, Oyesegun AR, Elumelu TN. Radiotherapy in the management of early breast cancer in Ibadan: outcome of chest wall irradiation alone in clinically nodes free axilla. *Afr J Med Sci* 2002;31:345–47.

40. Cuzick J, Stewart H, Peto R, *et al.* Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. *Cancer Treat Rep* 1987;71:15–29.

41. Cuzick J, Stewart H, Rutquvist 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.

42. Yarnold JR, Price P, Steel GG. Treatment of early breast cancer in the United Kingdom: radiotherapy fractionation practice. *Clin Oncol (R Coll Radiol)* 1995;7:223–26.

43. 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.

44. Perloff M, Lesnick GJ, Korzun A, *et al.* Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. *J Clin Oncol* 1988;6:261–69.

45. Ellis MJ, Coop A, Singh B, *et al.* Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for erbB-1- and/or erbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001;19:3808–16.

46. Prize P, Hoskin PJ, Easton D, *et al.* Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986;6:247–55.

47. Gaze MN, Kelly CG, Kerr GR, *et al.* Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiother Oncol* 1997;45:109–16.

48. Bone Pain Trial Working Party. 8Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomized comparison with a multifractionation schedule over 12 months of patient follow-up. *Radiother Oncol* 1999;52:11–21.

49. Steenland E, Leer JW, van Houwelingen H, *et al.* The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastases Study. *Radiother Oncol* 1999;52:101–9.

50. Salazar OM, Sandhu T, da Motta NW, *et al.* Fractionated half-body irradiation for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomized phase III trial of the IAEA. *Int J Radiat Oncol Biol Phys* 2001;50:765–75.

51. Sarin R, Budrukkar A. Efficacy, toxicity and cost-effectiveness of single-dose versus fractionated hemibody irradiation. *Int J Radiat Oncol Biol Phys* 2002;52:1146.

52. Lang FF, Sawaya R. Surgical treatment of metastatic brain tumors. *Semin Surg Oncol* 1998;14:53–63.