Radiation treatment for breast cancer

Recent advances

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ABSTRACT

OBJECTIVE To review recent advances in radiation therapy in treatment of breast cancer.

QUALITY OF EVIDENCE MEDLINE and CANCERLIT were searched using the MeSH words breast cancer, ductal carcinoma in situ, sentinel lymph node biopsy, and postmastectomy radiation. Randomized studies have shown the efficacy of radiation treatment for ductal carcinoma in situ (DCIS) and for invasive breast cancer.

MAIN MESSAGE Lumpectomy followed by radiation is effective treatment for DCIS. In early breast cancer, shorter radiation schedules are as efficacious for local control and short-term cosmetic results as traditional fractionation regimens. Sentinel lymph node biopsy is done in specialized cancer centres; regional radiation is recommended for patients with four or more positive axillary lymph nodes. Postmastectomy radiation has been shown to have survival benefits for high-risk premenopausal patients. Systemic metastases from breast cancer usually respond satisfactorily to radiation.

CONCLUSION Radiation therapy continues to have an important role in treatment of breast cancer. There have been great advances in radiation therapy in the last decade, but they have raised controversy. Further studies are needed to address the controversies.

RÉSUMÉ

OBJECTIF Passer en revue les récents progrès en radiothérapie dans le traitement du cancer du sein.

QUALITÉ DES DONNÉES Des recensions ont été effectuées dans MEDLINE et CANCERLIT à l'aide des termes MeSH en anglais pour cancer du sein, carcinome canalaire in situ, biopsie du ganglion lymphatique sentinelle et postmastectomie. Des études aléatoires ont démontré l'efficacité de la radiothérapie pour le carcinome canalaire in situ (CCIS) et pour le cancer envahissant du sein.

PRINCIPAL MESSAGE La tumorectomie suivie d'un rayonnement est une thérapie efficace pour le CCIS. Dans le cancer du sein en phase initiale, des intervalles de rayonnement plus courts sont aussi efficaces pour le contrôle local et des résultats cosmétiques à court terme que les régimes de fractionnement traditionnels. La biopsie des ganglions lymphatiques sentinelles est effectuée dans les centres anticancéreux spécialisés; l'irradiation régionale est recommandée chez les cas présentant quatre ganglions lymphatiques axillaires positifs. Il a été démontré que le rayonnement postmastectomie présentait des avantages en termes de survie chez les patientes à risque élevé en préménopause. Les métastases systémiques d'un cancer du sein réagissent habituellement de manière satisfaisante au rayonnement.

CONCLUSION La radiothérapie continue d'exercer un rôle important dans le traitement du cancer du sein. Il s'est produit des progrès considérables en radiothérapie au cours de la dernière décennie, mais ils ont soulevé des controverses. D'autres études sont nécessaires pour répondre à ces controverses.

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Radiation therapy continues to play an important role in treatment of women with breast cancer, which can range from ductal carcinoma in situ (DCIS) to invasive breast cancer and metastatic disease. There have been great advances in radiation therapy in the last decade, but controversy has arisen over both breast conservation measures and treating women after mastectomy. Breast cancer remains the most common cancer in Canada. Family physicians have a crucial role in screening for breast cancer and in educating women about recent advances and controversies in treatment.

Quality of evidence

Generally good evidence from randomized controlled trials supports use of radiation with breast-conserving surgery and for high-risk women after mastectomy. We conducted a search of MEDLINE from January 1966 to October 2001 and CANCERLIT from January 1983 to October 2001 using the MeSH words breast cancer, ductal carcinoma in situ, sentinel lymph node biopsy, and postmastectomy radiation.

Ductal carcinoma in situ

With widespread use of screening mammograms, the age-adjusted incidence of DCIS has increased more than five-fold in the last two decades.[1] Treatment options for DCIS range from mastectomy to lumpectomy followed by radiation therapy to excision alone. Mastectomy cures more than 95% of patients with DCIS.[2] Breast-conservation therapy has been used for patients with DCIS and those with early-stage invasive breast cancer. In fact, it might be contradictory to breast preservation to offer lumpectomy and irradiation to women with invasive disease but mastectomy to patients with DCIS. No trial, however, has compared the effectiveness of mastectomy and lumpectomy plus radiation for patients with DCIS.

The natural history of DCIS after lumpectomy alone is that subsequent local recurrences tend to be equally divided between invasive disease and DCIS. The National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized 818 women with DCIS to excision alone or excision plus radiation. At 90 months' follow up, recurrence of invasive disease decreased from 13% to 4% and recurrence of DCIS decreased from 13% to 8% with the addition of radiation therapy.[3] Studies are ongoing to examine the role of tamoxifen and to identify patients with DCIS who could be treated with excision alone.[4]

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Invasive disease

Early breast cancer. Prospective randomized trials comparing mastectomy with lumpectomy plus radiation have all shown similar survival rates with both methods.[5-10] Again in these trials, researchers attempted to identify patients with characteristics indicating they did not need breast irradiation. Previous trials have shown that, even with small invasive tumours (≤1 cm), recurrence of breast cancer decreased from 21% to 11% with postoperative adjuvant radiation.[11] Breast irradiation, therefore, continues to be recommended after conservative surgery for all patients. The benefits and side effects of radiation, however, have to be explained to patients. Recent evidence suggests that, for node-negative breast cancer patients, combined tamoxifen and radiation result in fewer local recurrences than tamoxifen alone.[12]

A recent trial in Ontario tried to address how to use more rapid fractionation to shorten the length of treatment. Patients were randomized to receive either 50 Gy in 25 fractions or 42.5 Gy in 16 fractions. Local control and cosmetic results at 5 years were similar in the two arms,[13] but long-term results are pending.

After breast-conserving surgery, most recurrences are in the same quadrant as the initial invasive tumour.[14,15] This led researchers to examine whether brachytherapy (radiation implant) alone is adequate. The potential advantages of brachytherapy are that it allows delivery of a high dose of radiation to the central tumour bed and quick completion of therapy.[16-19] We await results from ongoing trials.

Nodal irradiation: sentinel lymph node biopsy. Despite the promise of tumour-associated prognostic factors, such as hormone receptors, ploidy, S phase, and oncogene expression, involvement of axillary lymph nodes is still the best prognostic indicator in breast cancer. It also continues to be an important guide for use of systemic adjuvant therapy, especially for small tumours. Axillary lymphadenectomy, however, is not without complications. Complications include altered sensation of the upper inner aspect of the arm, restriction of shoulder movement, seromas on the wound, vascular injury, brachial plexus injury (rare), and the more common lymphedema of the arm.

Sentinel lymph node (SLN) biopsy was developed to assess cancer stage accurately without removing most of the axillary contents. The first step along the route of lymphatic drainage from a primary tumour is finding a limited set of regional lymph nodes. Dyes, radiographic contrast agents, and radioactive tracers have been used to identify these lymph nodes, termed sentinel nodes.

In 1992, Morton et al[20] used a blue dye to identify the lymphatic duct that drained into the sentinel nodes of patients with melanoma. In 1993, Krag et al[21] reported using a hand-held gamma probe intraoperatively to find axillary "hot spots" (corresponding to SLNs) and remove hot nodes until the axillary background count fell below a defined threshold. Giuliano et al[22] reported identifying blue lymphatic vessels exiting the tail of the breast and tracing them to a blue-stained SLN in the axilla and removing all blue nodes.

All blue or hot nodes are examined by pathologists. This procedure is best validated by a backup axillary dissection after removal of SLNs. The level of expertise in this procedure varies from institution to institution and surgeon to surgeon.

Recent Canadian clinical practice guidelines still emphasize that axillary dissection is the standard of care for surgical staging of operable breast cancer.[23] If patients request or are offered SLN biopsy, the benefits and risks and what is and is not known about the procedure should be explained. A positive SLN biopsy result or failure to identify a SLN should prompt full axillary dissection. Sentinel lymph node biopsy should not be performed by surgeons who rarely do breast-cancer surgery and is contraindicated in women who have clinically palpable nodes, locally advanced breast cancer, or multifocal tumours, or have had previous breast surgery or previous breast irradiation. The American Society of Breast Surgeons[24] recommends that reasonable competence for surgeons performing SLN biopsies is reached when they have performed 30 SLN biopsies followed by complete axillary dissection with an 85% success rate and a 5% or lower false-negative rate in identifying SLNs. Of these 30 cases, at least 10 should have metastatic disease in the axilla.[24]

To test the safety and efficacy of SLN biopsy in breast cancer, the National Cancer Institute has sponsored a phase 3 prospective randomized clinical trial, the NSABP B-32 trial. Eligible patients will be randomized to two treatment arms: group 1 will receive SLN biopsy followed by level 1 and 2 axillary node dissection (standard therapy); group 2 will have SLN biopsy and go on to axillary dissection only if metastatic disease is identified on pathologic evaluation of SLNs (study arm). Patients in both arms who are sentinel node–negative will be compared as to disease-free overall survival, regional recurrence rates, arm morbidity, and quality of life.[23] If this trial confirms that SLN biopsy is equivalent to axillary dissection, surgeons and patients can be assured that any recurrences following these procedures are likely due to the underlying biology of the disease rather than the type of surgical procedure used.[25]

Axillary radiation or axillary dissection? No prospective randomized trials are currently testing the efficacy of axillary radiation following positive results from SLN biopsy without complete dissection. Axillary dissection still remains standard therapy. Regional radiation is recommended for patients with four or more positive axillary lymph nodes.

Postmastectomy irradiation. Use of postmastectomy radiation has been discussed extensively during the last several years. Its ability to influence survival has remained controversial for years. In 1997, two randomized trials, the Danish Breast Cancer Cooperative Group Trial[26,27] and the British Columbia Trial[28,29] reported significant survival advantages in high-risk premenopausal patients who received comprehensive irradiation to the chest wall, supraclavicular fossa, axilla, and upper internal mammary nodes in addition to chemotherapy. This supports the notion that adjuvant radiotherapy affects survival in breast cancer. The role of postmastectomy radiation therapy for patients with one to three positive axillary lymph nodes is currently being evaluated in a randomized intergroup trial.

Metastatic breast cancer

Symptoms of metastatic breast cancer usually respond well to radiation for palliation. Previous trials have suggested that patients with bone metastases from primary breast cancer often get pain relief from palliative radiotherapy.[30-32]

Side effects of radiotherapy

When women with breast cancer are presented with treatment options, they must be informed of the acute and late complications of radiotherapy. Skin erythema and fatigue are common short-term side effects; both symptoms usually resolve completely within 3 to 6 months. During the first 2 years after surgery and radiotherapy, about 20% of patients experience intermittent pain in their breasts. Lasting cosmetic sequelae of irradiation might become visible after the first year and might last for several years in a few patients (1% to 8%) who suffer from severe acute skin reactions.

Severe long-term ill effects of radiation are rare, but can include pneumonitis (0.7% to 7%), pericarditis (0 to 0.3%), rib fracture (1.1% to 1.5%), brachial plexopathy (0 to 1.8%), and noticeable arm edema

(1%) that increases in incidence along with axillary lymphadenectomy.[33] Studies show a significantly higher death rate due to myocardial infarction in patients with left-sided tumours than in patients with right-sided tumours.[34,35] Radiation can also be carcinogenic, although the incidence is rare (0.1% to 0.2% per decade of follow up).

Patient selection for radiotherapy

Although many prospective randomized trials show similar local tumour control and survival rates with breast-conservation therapy plus radiation and with modified radical mastectomy, not every breast-cancer patient is eligible for conservation therapy. Absolute contraindications include[36]:

- first or second trimester of pregnancy,
- more than two primary tumours in separate quadrants,
- diffuse microcalcifications,
- an extensive intraductal component with positive margins,
- previous breast radiation, and
- an inability to lie flat or abduct the arm.

Relative contraindications include:

- large tumours in small breasts,
- collagen disease, and
- very large breasts (morbid obesity).

Conclusion

Radiation therapy is playing an increasingly important role in management of breast cancer. Clinical trials are ongoing to address unresolved issues. Participation in clinical trials should remain a priority for women with breast cancer. Outside clinical trials, management of patients should include well-informed shared decision making about therapy.

Competing interests

None declared

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Editor's key points

- Good evidence suggests that lumpectomy followed by radiation is as effective as mastectomy for invasive cancer and ductal carcinoma in situ.
- Radiation is currently recommended as an alternative to axillary node dissection when more than four sentinal nodes are positive.
- Regional radiation is recommended for patients with four or more positive axillary lymph nodes.
- Metastatic breast cancer symptoms, such as bone pain, respond well to radiation.

Points de repère du rédacteur

- De bonnes données probantes font valoir que la tumorectomie suivie d'un rayonnement est aussi efficace qu'une mastectomie pour un cancer envahissant et un carcinome canalaire in situ.
- Le rayonnement est actuellement recommandé comme solution de rechange à la dissection des ganglions axillaires lorsque plus de quatre ganglions sentinelles sont positifs.
- L'irradiation régionale est recommandée pour les patientes présentant quatre ganglions lymphatiques axillaires positifs ou plus.
- Les symptômes du cancer métastatique du sein, comme les douleurs dans les os, répondent bien au rayonnement.

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