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Review

Breast conservation in the 21st century

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Abstract

As breast cancers are diagnosed at increasingly early stages, and there is little biological rationale for mastectomy in most patients, breast conservation is likely to be practised with increased frequency in the future. Newer breast imaging techniques, particularly magnetic resonance imaging (MRI), should contribute to improved pretherapy planning, both aiding in the selection of patients for conservation approaches, and estimating the residual tumour burden following minimally invasive surgical interventions. Image-guided tumour mapping may permit local treatment to be individualised, most importantly allowing definition of subgroups not requiring treatment directed at the whole breast. Moreover, interventional radiology opens new possibilities for focalised treatments, which may come to be employed in the management of small lesions. The increasing use of primary chemo- or chemoendocrine therapy will also tend to favour the option of breast conservation. Functional imaging techniques, including MRI, may prove valuable in the assessment of response to medical therapy, allowing more individualised use of radiotherapy and surgery. Technical progress and the development of biological response modifiers may further improve the therapeutic ratio associated with radiation treatment.

Keywords: Breast carcinoma; Breast conservation; Magnetic resonance imaging; Radiotherapy; Minimally invasive surgery

1. Introduction

The management of breast cancer has made significant strides during the last decades of the 20th century. These advances, whose legitimacy rests solidly on consistent evidence from randomised trials, can be reduced to three major paradigms: firstly, that early detection by mammographical screening can reduce breast cancer mortality [1]; secondly that adjuvant systemic therapy can delay or prevent recurrence and thereby improve survival rates [2,3]; and thirdly that total mastectomy does not convey a survival advantage in comparison with strategies allowing preservation of the breast [4]. The safety of breast conservation has progressively gained acceptance, so that the combination of wide local excision and breast irradiation (breast-conserving therapy, BCT) is currently considered the preferred choice in patients with stage I and II disease [5]. Although putative contraindications to BCT concern only a small minority of patients, its use none the less varies considerably according to patient age, tumour size and geographical region [6]. This reflects, among other things, both variability in surgical preferences and the perceived inconvenience of undergoing a prolonged course of radiotherapy, which is generally prescribed following breast-conserving surgery, at least for invasive carcinoma. In certain Western European regions, conservation surgery accounts for more than 70% of all operations in breast cancer patients, all stages combined [7,8]. Considering the pre-eminence enjoyed by total mastectomy only two decades ago, this is indeed an impressive achievement.

At the beginning of this new century, it seems appropriate to speculate about future practices. Are they going to remain essentially unchanged from today's gold standard of lumpectomy with postoperative whole-breast irradiation? What are the implications of screening and improved breast imaging for BCT? Will systemic treatment practices have any influence on breast preservation? Will developments in radiotherapy affect how BCT is practised? It is these authors' opinion that things are likely to change significantly in the next two decades. This paper hopes to stimulate discussion among a multidisciplinary readership as to how changes

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may be implemented to the greatest benefit of our patients.

2. Impact of medical imaging on selection for breast conservation

The potential impact of imaging on breast-conserving practices is only partially felt today. Since mammography is being implemented more and more widely in asymptomatic women, it can be expected that the breast cancer population will become increasingly skewed toward patients with intraductal carcinoma (DCIS) and early invasive tumours, with a corresponding reduction in more advanced cases. Although this has already led to an increase in the proportion of tumours amenable to conservation surgery, this trend can be expected to become more pronounced over the coming years. Moreover, imaging not only increases the number of patients benefiting from conservation approaches, but should also influence the way in which breast conservation is practised. Of course, mammography is already used at time of diagnosis to screen for multicentricity and bilaterality in order to optimise surgical treatment. However, even with special techniques such as spot compression and magnification views, mammography provides only limited assurance that an apparently unifocal tumour is in fact circumscribed.

Additional tools, such as sonography and magnetic resonance imaging (MRI) may prove to be valuable in planning the surgical approach in cases where breast preservation is desired. Although useful as a complement to mammography in the delineation of invasive tumour foci, sonography is relatively insensitive to the presence of *in situ* lesions [9]. This is a serious limitation, as intraductal extension is an important mechanism of local failure. Although MRI demonstrated sensitivities of 94–100% for the detection of invasive cancer, the sensitivity of MRI for purely intraductal lesions varies from 77% [10] to 94% [11]. Because the diagnosis of breast cancer with MRI is based on abnormal contrast enhancement related to angiogenesis with abnormal vessel permeability, lesions without this histopathological feature will not be detected and this remains a definite limitation of MRI. Another important limitation of MRI is its low specificity [12]. False-positive findings are due to overlapping MRI features between benign breast tissue abnormalities and pre-invasive cancer. The recent development of interpretation algorithms and the standardisation of lesion description through the development of a breast MRI lexicon is hoped to improve the specificity and reproducibility of this technique [13].

Despite these limitations, MRI is considered an excellent imaging tool for determining tumour volume and extent preoperatively. In a recent review, Davis and McCarty summarised seven studies comparing the maximal pathological tumour diameter with that assessed by imaging modalities [14]. MRI correlated best with pathology (correlation coefficient of 0.94–0.98), compared with mammography (0.46–0.77) or sonography (0.45–0.84). The superiority of MRI was particularly evident in premenopausal women and in patients assessed after chemotherapy. Multifocality detected by preoperative MRI has shown good correlation with histological examination of serially sectioned mastectomy specimens [12,15]. For the diagnosis of multicentricity, often considered a contraindication to breast conservation, the 95% sensitivity of MRI was significantly higher than the 57% sensitivity of mammography [14,16]. However, MRI had a 12% false-positive rate, whereas there were no false-positive findings with mammography.

Although the cost-effective use of MRI in preoperative staging has not yet been studied, the increased knowledge of tumour extent, multifocality and multicentricity will almost inevitably influence surgical decision making and patient preferences for different treatment options. However, at the present time it is unknown to what degree this information should be allowed to modify treatment practice. A real danger exists that the additional anatomical information provided by MRI will be used uncritically, with a resulting explosion of cosmetically unfavourable wide resections and an increasing number of potentially unnecessary mastectomies. The function of radiotherapy is to treat residual cancer foci (or precancerous changes) remaining after local tumour excision, and in the total absence of such changes breast irradiation presumably serves no useful purpose. Studies are underway in the UK to assess prospectively the clinical importance of MRI findings in patients whose therapy had not been allowed to be influenced by the MRI results [17,18]. Only through such prospective studies can a scientifically sound and cost-effective implementation of this costly new technology be assured.

3. Selection of patients for 'focalised' treatment

The potential impact of imaging on BCT, however, is much more profound than simply improving selection for conservation surgery. Despite evidence that early breast cancer frequently presents as a segmental disease, standard treatment strategies are almost uniformly directed at the entire breast. Meticulous pathological studies indicate that a substantial proportion of T1/T2 cancers are associated with tumour foci that do not extend beyond 1 cm from the macroscopic edge of the index lesion [19]. Although histopathological features, including margin status, may be of some use in reliably identifying patients having unifocal tumours, it is possible that advanced imaging techniques will have an

Table 1
Theoretical model of individualising breast conservation by employing optimised breast imaging (e.g. MRI)[a]

Group 1. Unifocal tumour on preoperative imaging. No apparent residual cancer after lumpectomy: no further therapy to the breast.
Group 2. Minimal local tumour extensions within 2 cm of tumour mass: lumpectomy with adjuvant focalised therapy to the involved quadrant (e.g. brachytherapy, intra-operative electron beam).
Group 3. Small-volume tumour extensions (multifocality, multicentricity) beyond 2 cm of tumour mass: lumpectomy with adjuvant whole-breast radiotherapy.
Group 4. Larger-volume tumour extensions (multifocality, multicentricity) beyond 2 cm of tumour mass: total mastectomy.

[a] Patients are assumed to have appropriate systemic therapy.

important contribution to make in this regard. This would potentially allow confident selection of patients for truly focalised treatments, without requiring the (most frequently) superfluous amputation or irradiation of breast tissue outside of the involved segment. A possible innovative approach integrating imaging results into clinical decision making is illustrated in Table 1.

The performance of MRI in diagnosing the extent of residual disease after gross tumour excision varies among different studies. Orel and colleagues reported an accuracy of 64% for the diagnosis of residual breast cancer with MRI compared with 7% with mammography in 47 patients undergoing postoperative imaging within a mean time of 18 days after initial surgery [20]. Soderstrom and associates reported an accuracy of 84% in 18 patients seen within 10 months after initial surgery [21]. Differences within studies might correspond to differences in the percentage of DCIS (not stated in [21]) or to differences in the time interval between initial surgery and subsequent MRI. Frei and colleagues recently demonstrated a positive relationship between the specificity of MRI and the time interval between initial lumpectomy and MRI [22]. False-positive findings due to postsurgical inflammation could be avoided when patients underwent MRI later than 1 month after surgery. Even for evaluating residual tumour after excision of intraductal carcinomas, MR imaging was found to have a accuracy of 88% in a series of 38 patients diagnosed with DCIS (K. Kinkel, University of California, San Francisco, CA, USA). These data suggest that MRI may prove to be useful in the selection of favourable patients who might not require whole-breast irradiation.

4. Options for focalised treatment

Focalised treatments (i.e. therapy limited to the tumour-bearing quadrant, Table 2) obviously include wide excision alone, but selection of appropriate low-risk patients based on clinical and pathological criteria has proven unexpectedly problematic [23]. As failure after local excision is most commonly within or adjacent to the tumour bed, combining lumpectomy with localised irradiation of the excision site might appear promising. However, in unselected patients external electron beam treatment of the tumour area led to disappointing results in a randomised trial in comparison with whole-breast treatment [24]. Interstitial radioactive implantation (brachytherapy) is an attractive approach, and selected patients have been successfully managed in this fashion [25]. Other techniques being tested for focalised irradiation of the tumour bed area include the use of intra-operative electron beams (R. Orecchia, European Cancer Institute, Milan, Italy), and a low-energy X-ray generator that can be inserted to irradiate the excision cavity in the operating theatre [26].

In addition, experience with image-guided core biopsy techniques has led to new possibilities in focalised treatment that involve neither surgical excision nor ionising radiation. These include the direct removal of small lesions using the biopsy instrument [27], as well as focalised destruction of tumour tissue using radiofrequency probes [28], laser [29] or cryosurgery [30]. Whatever the methodology, non-surgical focalised techniques will need to be subjected to extensive preclinical and clinical testing. Such testing will serve to define selection criteria for focalised treatment and must demonstrate a high level of efficacy for the method under investigation. Only after efficacy has been demonstrated histologically in resection specimens of patients 'pretreated' with focalised techniques can such new approaches be confidently introduced into clinical practice. A healthy scepticism will be required in order to discourage the indiscriminate use of these techniques in inappropriate cases.

Table 2
Possible focalised (i.e. limited to involved quadrant) approaches to treatment of small unifocal breast cancers

After surgical excision:
Interstitial brachytherapy
Intra-operative electron beam
Low-energy X-ray 'radiosurgery'
In place of surgical excision:
Percutaneous excision with biopsy instrument
Cryotherapy
Radiofrequency hyperthermia
Laser hyperthermia

5. How might systemic therapy practices impact on breast conservation?

As a consequence of studies demonstrating their efficacy in a wide range of indications, both chemotherapy and hormonal treatment are included in the initial treatment programme for an increasing proportion of breast cancer patients. In patients treated with conservation surgery and breast irradiation, the use of both postoperative chemotherapy and tamoxifen has clearly led to a decrease in local failure, and good local control can usually be obtained even in high-risk patients [31]. For example, microscopic excision margin status may have limited value in patients receiving both breast irradiation and chemoendocrine therapy [32]. Combined-modality treatment may negate the utility of the assessment of multiple 'risk factors' purportedly defining patients in whom BCT might be 'unsafe'.

Because the decision regarding systemic therapy can be based on clinical and biopsy data in most patients, there has been a tendency in recent years to favour administering chemo- or hormonal therapy prior to loco-regional treatment. Clinical trials have demonstrated that such 'neoadjuvant' regimens increase the percentage of patients with stages I–II breast cancer who can have BCT [33,34]. In addition, a certain proportion of patients with locally advanced disease can be accepted for breast-conserving surgery following response to primary systemic therapy [35].

The move away from surgery as the initial therapeutic step has raised a certain number of questions regarding local treatment in this new setting. Although local control following breast-conserving surgery and radiotherapy generally appears satisfactory after preoperative chemotherapy, results from one trial suggest that patients who were able to have lumpectomy only because of clinical response to chemotherapy tended to have higher local failure rates than patients who had already been considered candidates for BCT at the initial evaluation [34]. This suggests that chemotherapy-induced tumour regression might make the surgical assessment of cancer extension more difficult, thereby tending to increase the residual tumour burden in such patients. Moreover, palpable tumour masses will become impalpable in one-fourth to one-third of patients treated with neoadjuvant chemotherapy [33,34]. Not only does complete clinical response make the technique of conservative surgery more problematic, but it raises the question of selecting appropriate patients with excellent chemotherapy response to receive radical radiotherapy, reserving surgery for patients failing to be controlled by non-surgical management. Although this approach may appear attractive, published experience suggests that unselected treatment of complete clinical responders by radiotherapy without tumour excision leads to a rather high local failure rate [36]. Non-invasive methods for assessing tumour response would be helpful in this setting.

In contradistinction to X-ray film techniques that are based on differences in density, certain imaging processes reflect differences in metabolic activity and thus may be useful in discriminating malignant from benign tissue. In addition to MRI with gadolinium enhancement, other 'functional imaging' techniques include positron emission tomography (PET) with fluorodeoxyglucose, which reflects glucose metabolism [37]. Because of the potential utility of functional imaging in evaluating the response to non-surgical treatment, developments in this area promise to have a practical impact on breast conservation approaches. Initial experience with contrast-enhanced MRI in patients receiving primary chemotherapy suggest a correlation of MRI findings with pathological response in 94–97% of cases [38,39]. PET imaging has also shown promising results in this setting [40]. If subsequent experience confirms that these imaging techniques are able to reliably assess response to primary chemotherapy or radiotherapy, such information might allow surgery to be used more selectively, as a function of the quality of response to the preceding treatment. This might also allow the option of breast preservation to be extended to patients currently not considered candidates for standard BCT.

6. Will developments in radiotherapy affect breast conservation?

If breast cancer were as radiosensitive (and as chemosensitive) as seminoma, surgery would have a minor place in the primary treatment of this disease. Breast carcinoma is a heterogeneous disease, in which some forms can be reliably eradicated by tolerable doses of X-rays, and others are so modestly radiosensitive as to limit the usefulness of this modality. Unfortunately, there is no convenient way to quantify the radiosensitivity of a breast cancer in a given patient. If predictive tests became available and were validated, they might allow radiotherapy to be used more selectively in situations where it is likely to be most effective [41,42]. In addition, identification of patients with excessive normal tissue radiosensitivity would encourage selection of such cases for alternative treatments, thus avoiding the occasional serious complications encountered following breast cancer radiotherapy [42]. Moreover, tumour radiosensitivity (as opposed to that of normal tissues) can potentially be increased selectively by chemical and biological agents [43], and there is reason to believe that such radiosensitisers may increase the effectiveness of breast cancer radiotherapy. Research into the molecular mechanisms of X-ray damage repair promises to lead to useful compounds in the not-too-distant future.

The accuracy of radiotherapy dose delivery has made considerable strides in the last 20 years. New technical developments, including three-dimensional conformal treatment planning [44], intensity modulated conformal X-rays [45] and proton beams [46], will enable the breast to be irradiated with optimal sparing of surrounding normal tissues, and may permit more precise focalised treatment of the tumour bed area as well. Whether or not breast irradiation will be a cost-effective use of such new technologies remains to be investigated by future research.

7. Conclusions

Improvements in breast imaging, increased use of primary systemic therapies, and refinements in radiotherapy are all likely to influence future approaches to the treatment of the breast in patients with apparently localised cancer. It is expected that breast conservation will not only become more prevalent, but that treatment approaches will be more individually tailored to the patient's oncological situation. It is important that local treatment questions continue to be addressed within the framework of future clinical breast cancer trials.

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