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Review

Intraoperative assessment of margins in breast conserving therapy: A systematic review

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ABSTRACT

Approximately one quarter of patients undergoing breast conserving therapy for breast cancer will require a second operation to achieve adequate clearance of the margins. A number of techniques to assess margins intraoperatively have been reported. This systematic review examines current intraoperative methods for assessing margin status. The final pathology status, statistical measures including accuracy of tumour margin assessment, average time impact on the procedure and second operation rate, were used as criteria for comparison between studies. Although pathological methods, such as frozen section and imprint cytology performed well, they added on average 20–30 min to operation times. An ultrasound probe allows accurate examination of the margins and delivers results in a timely manner, yet it has a limited role with DCIS where calcification is present and in multifocal cancer. Further research is required in other intraoperative margin assessment techniques, such as mammography, radiofrequency spectroscopy and optical coherence tomography.

Introduction

With a high association between ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC), ensuring clear margins during the resection of DCIS is part of the recommendations made by the National Breast Cancer Centre's evidence-based clinical practice guidelines [1]. Research has reported that 20–25% of patients treated for breast cancer using breast conserving therapy (BCT) will require a second operation to obtain clear margins, with second operation rates as high as 72% being reported [1–3]. Optimal surgical margin distance also varies between and within countries, with most reporting between 2 mm and 10 mm as the optimal minimum margin width [3–5]. As BCT is the preferred surgical method for patients who are not at high risk, the surgeon needs to accurately assess the extent of disease and margin status during surgery to reduce the risk of needing a second operation. A method that is able to provide the surgeon with accurate information intraoperatively about margin status would potentially reduce the need for a second operation by confirming all the cancer has been removed. An intraoperative margin assessment (IMA) method is defined for the purpose of this paper as a non-invasive method applied to the excised tissue or within the surgical cavity to produce results about margin status during surgery to enable further tissue shavings to be taken. The gold standard assessment will be defined as pathology (histology or cytology), performed post-operatively, and hereby referred to as the standard assessment.

This review will systematically select and analyse the literature to identify reported IMA methods in BCT for breast cancer. The objectives of this review are: (1) identify published academic literature, using a systematic method, that reports the use of an intraoperative method to determine margin status in BCT; (2) examine the level of concordance in margin assessment between reported IMA methods and standard assessment; (3) determine the accuracy of such methods; and (4) ascertain the impact on second operation rates. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines are used to structure the format and reporting of this review [6].

Methods

The databases Proquest, Medline, PubMed and Science Direct were searched on 3 June 2013 using the keywords: 'breast' AND 'surgery' AND 'intraoperative'. The inclusion criteria for articles

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were those which (1) examined DCIS of the breast or invasive breast cancer, (2) undertook an intraoperative assessment of the surgical margins with the intention of immediate feedback on the status (with or without further excision), (3) human studies only, (4) written in the English language, (5) scholarly journal article with full text available, and (6) published between January 2000 and May 2013. Articles were excluded from consideration if they: (1) used an additional shavings method to increase surgical margins without IMA, (2) examined lesion size, lesion localisation or guidance or specimen orientation without margin assessment, and (3) investigated various cancers outside of the breast.

Fig. 1 presents the process for study selection. In the first stage articles were extracted based on the search strategy outlined above. Article titles were reviewed by order of publication date (newest to oldest), blinding for author, journal, institution and country where the research was conducted. Articles were discarded if the title indicated the study clearly was not relevant to the purpose of this review. Potential titles were then compared to already selected articles for duplication and removed if appropriate. Next, the abstracts of selected papers were assessed against the eligibility criteria listed above, with blinding. Finally, full text articles were then assessed against the eligibility criteria listed above, with blinding. Reason for rejection was also documented.

A quality assessment tool to assess the strength of each article was developed based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort, case–control and cross-sectional studies (combined) [7]. Weighting was applied for each area according to the level of importance to give an overall quality assessment score (QAS) out of 20. The tool was initially tested by three reviewers on the first ten articles, and subsequently applied to all articles by the primary reviewer (first author) who solely performed the systematic review. Data items were then highlighted and extracted into result tables.

The principal summary measures to meet the objectives of this review are (1) IMA methods, (2) level of significance between reported IMA methods and standard assessment, (3) accuracy of IMA methods, or if unavailable the sensitivity and specificity, and (4) second operation rates, taking optimal margin width and study methodology into account. Only when the accuracy, sensitivity and specificity were not provided but the number of positive and negative cases by IMA and standard assessment were reported, the data were further analysed to estimate the accuracy, sensitivity, specificity, positive and negative predictive values. Because these studies varied in optimal margin width and detailed information was seldom provided, a meta-analysis of pooled data was not performed and risk of bias across studies could not be calculated.

Results

Study characteristics

As shown in Fig. 1, 27 studies were included in this review. Table 1 summarises the characteristics of these studies. The mean QAS was 12.19 (standard deviation [SD] 3.13) and ranged from 5.75 to 17.75. The studies varied greatly on their presentation of results, which impacted on the overall QAS assigned during the evaluation process.

One third (9/27) of the studies recruited subjects prospectively but did not act on results from IMA, i.e. prospective observational. About 40% (11/27) of studies also recruited prospectively and acted on IMA results, i.e. prospective experimental, whereas the remaining (7/27) studies were retrospective chart reviews. Optimal margin width ranged from zero to 5 mm (not reported in four studies), with five studies using $\geq$0 mm, seven using $\geq$1 mm, seven using $\geq$2 mm and four using $\geq$5 mm.

Most studies (20/27) used the IMA on the excised specimen, with five studies also examining within the surgical cavity. The majority of studies did not discuss methods for assessing multifocal cancers, with 8 (29.6%) studies analysing results by tumour instead of by case. Only two studies examined in the surgical cavity but not the excised specimen. Half (14/27) of the studies were undertaken in the United States of America (USA) and the majority of studies (21/27) were undertaken at one institutional site. Very few studies (3/27) reported the number of surgeons or users of the IMA method; consequently it is not feasible to comment on the risk of inter-operator variability.

The mean age of patients, where reported, were similar between studies, ranging from 55 to 60 years. Histological information, namely, type, grade and tumour size, were extracted to assess whether study populations were comparable. Most studies (19/22) reported that the majority of cases were invasive ductal carcinoma, while three studies recruited only DCIS cases. Although the cases were predominantly classified as grade II, there was little difference in the number of cases reporting grade I or grade III disease. The greatest variation in study characteristics was found in tumour size, with many studies (12/15) reporting a mean tumour size between 1 and 2 cm.

Table 2 and Table 3 present the reported summary measures. Data were analysed by study methodology as further shavings based on IMA findings were taken in prospective experimental studies, impacting on the final pathology margin status and second operation rates.

Prospective experimental studies

Based on the reported level of concordance, where the IMA method was compared to the standard assessment (pathology), the radiofrequency spectroscopy probe performed the best [10,22]. However, the 2-view specimen mammography and the macroscopic margin assessment technique, which had the largest optimal margin distance of $\geq$5 mm, reported the lowest second operation rates of 5% and 7.3%, respectively. The reporting of time difference was not reliable because comparisons were made against different procedures. The intraoperative digital specimen mammography (IDSM) reduced operation times by on average 19 min when compared to standard specimen mammography (SSM) [28]. 2-view specimen mammography reported an average 15 min increase in operation time when compared to the standard assessment [30]. Ultrasound could reduce operation time by 1 min [32] to 15 min [34], whereas frozen section increased operation time by 27 min on average [4].

Overall accuracy of IMA in prospective experimental studies was only reported for frozen section [11] (98.3%) and touch smear cytology [17] (93.8%). Sensitivity and specificity rates were given in half of the prospective experimental studies, with frozen section [11] reporting the highest sensitivity (91.1%) and specificity (100%). Interestingly, the other two studies which produced good sensitivity and specificity were also intraoperative pathological assessments. Touch smear cytology [17] reported 70% sensitivity and 97.1% specificity based on a sample size of 160 patients. Macroscopic margin assessment [29] reported sensitivity and specificity rates of 73% and 88%, respectively, in 220 cases.

Prospective observational studies and retrospective chart reviews

Several IMA methods performed well based on the reported level of concordance. Ultrasound [16,19] showed no significant difference ($p < 0.05$) to standard assessment, which supported the