



Tumor Resection Margin Definitions in Breast-Conserving Surgery: Systematic Review and Meta-analysis of the Current Literature

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Abstract

Worldwide, various guidelines recommend what constitutes an adequate margin of excision for invasive breast cancer or for ductal carcinoma-in-situ (DCIS). We evaluated the use of different tumor resection margin guidelines and investigated their impact on positive margin rates (PMR) and reoperation rates (RR). Thirteen guidelines reporting on the extent of a positive margin were reviewed along with 31 studies, published between 2011 and 2016, reporting on a well-defined PMR. Studies were categorized according to the margin definition. Pooled PMR and RR were determined with random-effect models. For invasive breast cancer, most guidelines recommend a positive margin of tumor on ink. However, definitions of reported positive margins in the clinic vary from more than focally positive to the presence of tumor cells within 3 to 5 mm from the resection surface. Within the studies analyzed (59,979 patients), pooled PMRs for invasive breast cancer ranged from 9% to 36% and pooled RRs from 77% to 99%. For DCIS, guidelines vary between no DCIS on the resection surface to DCIS cells found within a distance of 2 mm from the resection edge. Pooled PMRs for DCIS varied from 4% to 23% (840 patients). Given the differences in tumor margin definition between countries worldwide, quality control data expressed as PMR or RR should be interpreted with caution. Furthermore, the overall definition for positive resection margins for both invasive disease and DCIS seems to have become more liberal.

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Introduction

Breast-conserving surgery aims to remove the primary tumor with an adequate margin of healthy tissue while conserving as much healthy tissue as possible. To determine complete tumor resection, the margin of healthy tissue is evaluated by histologic examination. Here, the pathologist inks the resection surface and reports the closest distance between the inked surface and tumor cells. An inadequate tumor resection margin increases the risk for local recurrence of the tumor.¹⁻⁵ In these cases, successive surgery is

recommended to still obtain total tumor clearance. These extra surgeries have a significant physical and emotional impact on patients, result in delayed adjuvant therapy, and represent a financial burden on the health care sector.⁶ Therefore, the European Society of Breast Cancer Specialists (EUSOMA) requires that the target proportion of breast cancer patients receiving a second surgery for the primary tumor should be less than 10%.⁷

Whether the tumor resection margins are found to be positive or negative plays a key role in the decision for a second surgery. However, there is no consensus on what constitutes an adequate margin of excision. Various guidelines provide different recommendations on the definition of a positive resection margin. As a result, positive margin status for invasive breast cancer varies from a definition of tumor cells on the resection surface up to 4 mm to tumor cells within a distance of 5 mm from the resection edge. Definitions for positive margins that are being used for ductal carcinoma-in-situ (DCIS) vary from DCIS cells found on the resection surface to DCIS cells within a distance of 2 mm from the resection surface.

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Table 1 Guidelines on What Constitutes Adequate Tumor Resection Margin

Year of Publication	Guidelines	IDC	DCIS	Evidence	Country
2009	NICE ⁸		≥2 mm		UK
	NZGG ⁹	≥2 mm	≥2 mm	10-15	New Zealand
2012	S3-Leitlinie DKG and DGGG ¹⁶	≥1 mm	≥2 mm	8,9,17,18	Germany
	NABON ¹⁹	No ink on tumor over <4 mm surface	No ink on DCIS	20	Netherlands
2013	SIGN ¹⁰	≥1 mm	≥1 mm	17,18	Scotland
2014	SSO-ASTRO ²¹	No ink on tumor ^a		22,23	USA
2015	ESMO ²⁴	No ink on tumor	>2 mm	21	Europe
	St Gallen ²⁵	No ink on tumor		21,22	Austria/Germany
	ABS ²⁶	≥1 mm	≥1 mm		UK
	Institute National du cancer ²⁷		≥2 mm	28	France
2016	SSO-ASTRO-ASCO ²⁹		≥2 mm	30	USA
	NCCN ³¹	No ink on tumor		21	USA
	JBCS ³²	No ink on tumor		21	Japan

Abbreviations: ABS = Association of Breast Surgery at Royal College of Surgeons of England; DCIS = ductal carcinoma-in-situ; DKG and DGGG = Deutsche Krebsgesellschaft e.V. und Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; ESMO = European Society for Medical Oncology; IDC = invasive ductal carcinoma; JBCS = Japanese Breast Cancer Society; NABON = Nationaal Borstkanker Overleg Nederland; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence; NZGG = New Zealand Guidelines Group; PMR = positive margin rate; RR = reoperation rate; SIGN = Scottish Intercollegiate Guidelines Network; SSO-ASTRO = Society of Surgical Oncology—American Society for Radiation Oncology; SSO-ASTRO-ASCO = Society of Surgical Oncology—American Society for Radiation Oncology—American Society of Clinical Oncology.

^aThese guidelines apply to patients with invasive breast cancer treated with whole-breast radiotherapy. It cannot be extrapolated to patients with pure DCIS, to those receiving neoadjuvant chemotherapy or accelerated partial breast irradiation, or to those not receiving radiotherapy.

To gain better insight into the impact of a certain positive margin definition, we performed a meta-analysis of the reported definitions of tumor resection margins in the guidelines that are currently being used for breast cancer treatment. We furthermore evaluated the impact of a certain positive resection margin definition by analyzing the associated positive margin rates (PMR) and reoperation rates (RR).

Methods

Guidelines

A literature search for the guidelines currently in use was performed manually. Guidelines were found in references in the articles found for the meta-analysis. Also, PubMed and Embase were scanned for the key terms “breast cancer,” “guideline” and “margin.” Guidelines were thoroughly evaluated according to the arguments supporting their recommendation. Margin guidelines differ for invasive breast cancer and DCIS, and therefore the analyses were subdivided accordingly.

PMRs and RRs

A literature search for all clinical studies describing PMRs for breast cancer between 2011 and 2016 was conducted by a medical information specialist on September 7, 2016. The search was performed in PubMed, Scopus, and Embase (Ovid). Search terms used were “breast cancer,” “margin” and “reoperation.” All literature published from 2011 to 2016 was assessed. Studies for which full text was not available, studies not available in English, case reports, conference abstracts, reviews, and animal or phantom studies were excluded from the analyses. Studies that reported on invasive breast cancer and DCIS as one group of patients and studies that reported on results per margin and not per patient were also excluded.

Included studies reported at least a precise definition of when a margin is considered positive and a PMR. Data extracted from the included studies were as follows: patient and tumor characteristics,

treatment details, PMR, and RR for patients with a positive resection margin. Studies were categorized into 6 different groups according to positive resection margin definition: a positive margin defined as tumor cells on more than 4 mm of the resection surface (more than focally positive), a positive margin defined as tumor cells on the resection surface up to 4 mm (focally positive), a positive margin defined as tumor cells on the resection surface (ie, on ink), and a close margin, defined as tumor cells within a distance of 1 mm, 2 mm, and 3 to 5 mm from the resection edge. Studies reporting on more than one margin definition were used in multiple categories. Reoperation was defined as a subsequent surgery to obtain clearance of the margin after a reported positive resection margin.

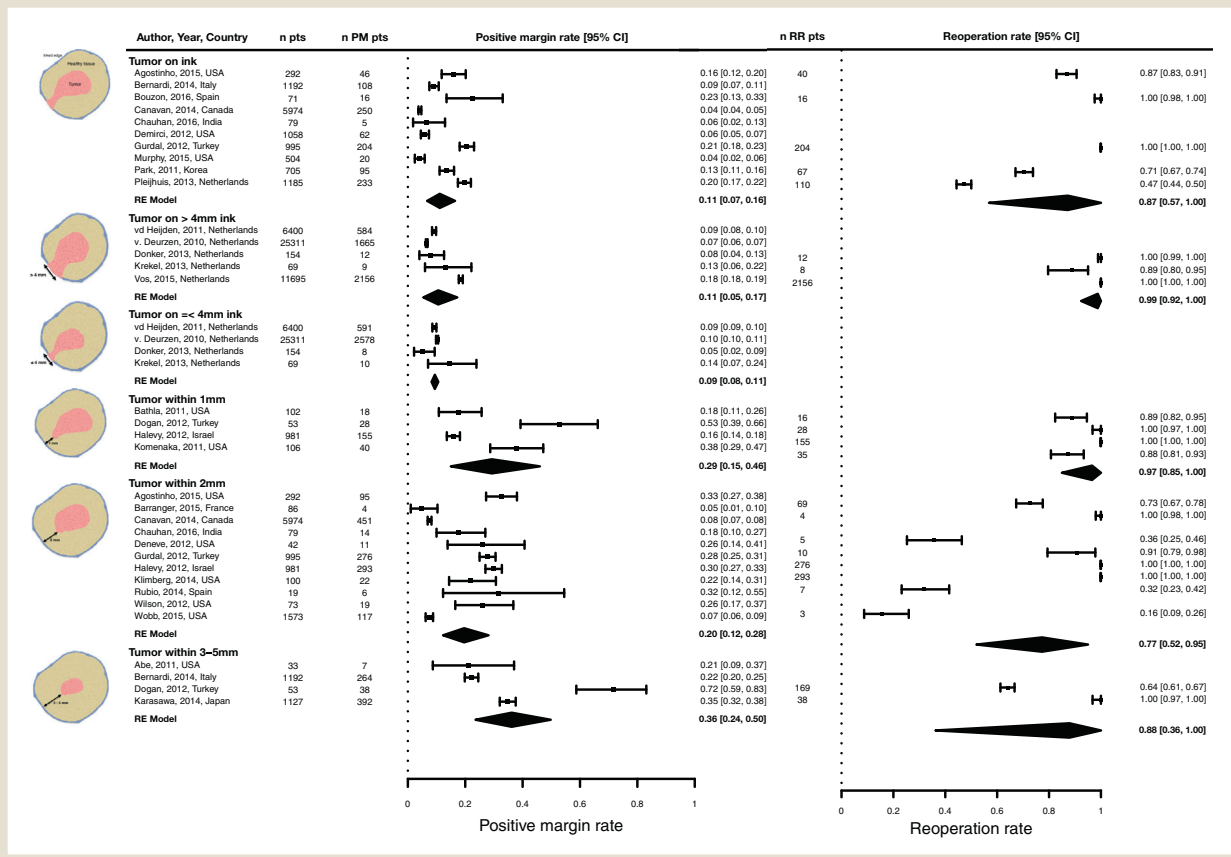
All outcome values were transformed by a Freeman-Turkey transformation to normalize and stabilize variance of the proportion sampling distribution. The transformed values were used in all meta-analyses random-effect models and then transformed back to show the pooled PMR and RR estimates. All models were fitted using the “metafor” package of RStudio 1.0.44 (2009-2016; RStudio, Boston, MA). By using random-effects models, the average chance for a positive resection margin after the initial surgery was calculated. The use of random-effects models was justified by the varying population characteristics between studies. At least 3 studies per category were required to obtain the estimated PMR and RR.

Results

We found 13 different guidelines, most of them national guidelines. Different definitions of positive resection margins were described (Table 1).

For the meta-analysis on the impact of positive margin definition on PMR and RR, the literature search resulted in 382 publications, of which 31 met the inclusion criteria. The studies included a total of 60,819 patients treated with breast-conserving surgery.

Figure 1 Positive Resection Margin Rate and Reoperation Rate for Tumor Cells on Ink. Positive Resection Margin Rate and Reoperation Rate Are Shown for Positive Resection Margin Defined as Tumor Cells on Ink, More Than Focally Positive, Focally Positive, Tumor Cells Within 1 mm, 2 mm, and 3 to 5 mm From Resection Surface, for Invasive Breast Cancer



Twenty-seven studies included 59,979 patients with invasive disease (invasive ductal carcinoma and invasive lobular carcinoma), and 4 studies included 840 patients with DCIS.

Patients for whom different margin extents were evaluated were included in more than one category. For invasive disease, the categories of the positive margin defined in the different studies as more than focally positive, focally positive, and tumor on ink included 43,629, 31,934, and 12,055 patients, respectively. The number of patients in the categories for tumor cells within a distance of 1 mm, 2 mm, and 3 to 5 mm from the resection edge were 1242, 10,214, and 2405, respectively.

For DCIS, the category of the positive margin defined as DCIS cells on the resection edge included 585 patients. The categories including the patients evaluated with a positive margin defined as DCIS cells within a distance of 1 and 2 mm from the resection edge included 307 and 533 patients, respectively.

For patients with positive margins, 18 studies reported on reoperations. Most studies (12/31) showed data from hospitals based in the United States.

Guidelines for Invasive Ductal Carcinoma

For invasive breast cancer, the definition of an adequate margin in the guidelines varies from the presence of a limited number of

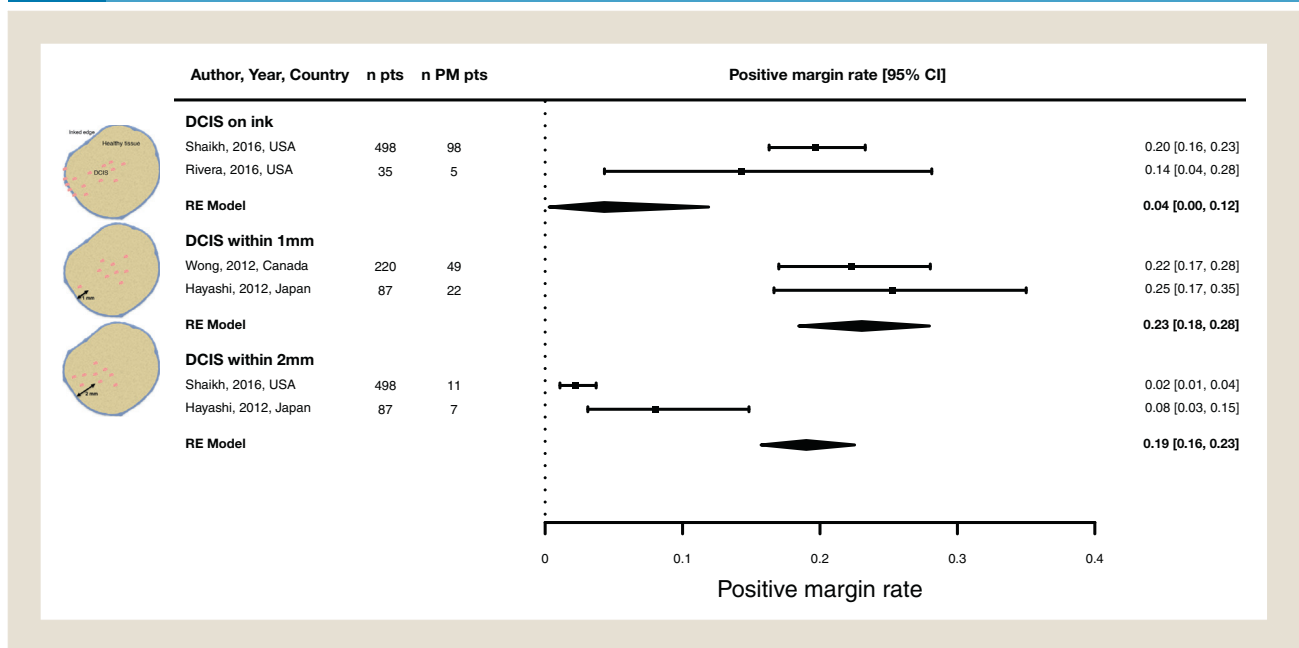
tumor cells on the margin (< 4 mm) to at least a tumor cell—free area of 1 or 2 mm from the edge of the excised specimen (Table 1).

The current Society of Surgical Oncology (SSO)-American Society for Therapeutic Radiology and Oncology (ASTRO) guidelines define an adequate resection margin as no tumor cells found on the resection surface for patients treated with whole-breast radiotherapy.²¹ Their recommendation is supported with the meta-analysis of Houssami et al²² disclaiming a significant evidence of a decrease in local recurrence when the margin increases. To show that a positive resection margin specifically defined by no tumor cells on ink is sufficient when combined with radiotherapy, the SSO-ASTRO referred to the NSABP B06 trial. In this large randomized trial, patients with negative margins, defined as no ink on tumor, showed a local recurrence of 14.3% when they were treated with lumpectomy combined with breast irradiation compared to 39.2% when lumpectomy was performed without radiation over a follow-up period of 20 years.²³ The SSO-ASTRO guidelines are used as the foundation for several national (National Comprehensive Cancer Network [NCCN], Japanese Breast Cancer Society [JBCS]) and European (European Society of Medical Oncology [ESMO], St Gallen) guidelines.^{24,25,31,32}

The Dutch guidelines take into account whether tumor cells are present on the resection surface. However, the extent of the involved surface determines which further treatment is to be offered

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Figure 2 Positive Resection Margin Rate and Reoperation Rate for DCIS on Ink and DCIS. Positive Resection Margin Rate and Reoperation Rate Shown Are for Positive Resection Margin Defined as DCIS on Ink, and DCIS Within 1 and 2 mm From Resection Surface for DCIS^{4,11-15,18,20,28,34-56}



Abbreviation: DCIS = ductal carcinoma-in-situ.

to the patient.¹⁹ Successive surgery is only recommended if more than 4 mm of the specimen’s surface is involved. In case of focally positive margins (defined as a resection margin involved up to 4 mm), an extra radiation boost is delivered.

The guidelines of the Association of Breast Surgery at Royal College of Surgeons of England (ABS) and the Scottish Intercollegiate Guidelines Network (SIGN), both from Great Britain, define a positive resection margin as tumor cells present within 1 mm of the surface.^{10,26} The ABS based its definition on a session at its conference in 2015 and choose a 1 mm margin as a “pragmatic and easy to interpret” approach.²⁶ SIGN based its guidelines on an earlier publication of the meta-analysis of Houssami et al,¹⁷ which stated that a low risk of local recurrence is associated with a positive margin of 1 mm. The evidence for a lower local recurrence risk with margins larger than 1 mm was too weak for SIGN to recommend a margin larger than 1 mm.^{10,17}

In New Zealand, a positive resection margin is defined as tumor cells within 2 mm of the resection surface, which is based on the expert opinion of the Guideline Development Team.⁹

Guidelines for DCIS

For DCIS, the definition of an adequate margin varies from no tumor cells on the resection surface to a tumor cell-free area of 2 mm from the resection surface (Table 1).

The recently published guidelines of the SSO-ASTRO-American Society of Clinical Oncology (ASCO) recommend the use of a 2 mm margin as the standard for an adequate margin in DCIS treated with whole-breast irradiation, as this is associated with lower rates of recurrence.²⁹ They base their recommendation on the statistical evidence provided by Marinovich et al.³⁰ Using two

alternative but complementary meta-analyses, they showed a reduction in local recurrence for a margin of 2 mm compared to smaller margins. No evidence was found that margins wider than 2 mm were associated with a further reduction in local recurrence in women receiving radiotherapy. The ESMO, National Institute for Health and Care Excellence (NICE), the German S3 Leitlinie, French, and New Zealand Guidelines Group (NZGG) guidelines all align with the positive resection margin definition of the SSO-ASTRO-ASCO.^{8,9,16,24,27}

The Dutch guidelines require reexcisions only when DCIS cells are found on the resection surface.¹⁹ In contrast to invasive breast cancer, these guidelines do not differentiate between focally positive and more than focally positive margins.

Both ABS and SIGN recommend a 1 mm margin for DCIS.^{10,26} ABS’s decision was based on their conference in 2015. SIGN decided to use the meta-analysis of Dunne et al³³ to support the decision to define a positive resection margin for DCIS as tumor cells within 1 mm. Dunne et al showed that a margin wider than 1 mm did not conclusively result in a lower local recurrence rate.

PMRs and RRs

Invasive Ductal Carcinoma. Figure 1 shows the pooled PMR and RR for the different definitions of a positive resection margin for invasive breast cancer.

For the 59,979 invasive breast cancer patients with positive margins defined as tumor on ink, more than focally positive and focally positive margins as well as PMRs were 11%, 11%, and 9%, respectively. For close margins defined as tumor cells within a distance of 1 mm, 2 mm, and 3 to 5 mm from the resection edge, PMRs were 29%, 20%, and 36%, respectively.

In the studies that reported on patients with a focally positive margin, patients did not undergo reoperation but received radiotherapy instead. In the categories of a positive margin defined as more than focally positive and tumor within a distance of 1 mm from the resection surface, almost all patients underwent a subsequent surgery (99% and 97%, respectively). In the case of tumor cells on the inked resection edge, 87% underwent a second surgery. Increasing the margin definition to a distance of 2 mm and 3 to 5 mm changed the RR to 77% and 88%, respectively.

Ductal Carcinoma-In-Situ. Figure 2 shows the pooled PMR for the different definitions of a positive resection margin for DCIS. For the 840 DCIS patients with positive margins defined as DCIS cells on the inked resection edge, and within a distance of 1 mm and 2 mm from the resection edge, the pooled PMRs were 4%, 23%, and 19%.

There was not enough data available to determine estimates for RR in the DCIS category.

Discussion

This meta-analysis provides an overview of the different guidelines reporting on the extent of a positive margin and the consequences of different definitions of a positive margin for the clinical practice. Helped by the fact that guidelines differ between countries worldwide, we found that uncertainty remains about the optimal extent of a positive margin. However, we have seen a more liberal policy for both invasive disease and DCIS over the last years.

The SSO-ASTRO guidelines define a positive margin as invasive breast cancer cells on the resection surface. These guidelines were supported by a large meta-analysis and were used as a reference to support other guidelines. As may be expected, because of the more liberal criteria, the PMR found in our study is low in this tumor on ink category (11%). When the margin is defined even more liberally, as focally positive and more than focally positive, the PMRs were comparable, at 9% and 11%, respectively. As the margin is defined more stringently toward a 1 mm, 2 mm, and 3 to 5 mm tumor-free margin, the percentage of patients with positive margins increased, as may be expected, to 29%, 20%, and 36%, respectively.

Clearly, RR after breast-conserving surgery for invasive breast cancer and for DCIS is affected by the definition used for what constitutes a positive margin. For invasive breast cancer, patients with a margin defined as more than focally positive and tumor cells within a distance of 1 mm from the resection edge were reoperated in 99% and 97% of cases. Surprisingly, according to our analysis, not all patients for whom tumor cells were found on ink underwent reoperation (87%). There are many reasons why reexcision may not have been performed, including limited amounts of tumor in proximity to the margin, lack of any breast tissue left to remove, and the expected effect of radiotherapy. For more stringent margin definitions of 2 mm and 3 to 5 mm, the percentage of patients undergoing reoperation after breast-conserving surgery decreased to 77% and 88%, respectively. Those patients were treated more often with radiotherapy.

Our data show that as a result of the different definitions of a positive margin used worldwide, the numbers on positive margins

and reoperations can hardly be used as an indication for quality of surgery across borders. For example, a country reporting on a higher PMR does not necessarily mean that the surgeons in that country perform worse. The definition of the positive margin might have been very strict, with the presence of tumor cells found within up to a few millimeters from the resection surface. As a consequence of this strict definition, the number of tumor-positive margins is high, as is the number of reoperations, without considering the surgical quality of care. For instance, in the United States patients with tumor cells on the resection surface are operated again, while in the Netherlands reoperations are only performed when tumor cells involve more than 4 mm of the resection surface. The fact that reoperations will be less often performed in the Netherlands does not necessarily mean that the quality of the primary surgery is better than in the United States.

In conclusion, our meta-analysis shows that the uncertainty about the optimal extent of a positive margin remains. As a consequence, quality control data expressed as the number of positive resection margins or number of reoperations should be interpreted with caution, given regional differences in margin definition and local policies for reoperation or radiotherapy. However, we found that the policy regarding the definition of a positive margin for both invasive disease and DCIS has become more liberal.

Disclosure

The authors have stated that they have no conflict of interest.

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