

Pathological examination for quality assurance in breast conserving therapy for breast cancer

Thomas Decker,¹ Monika Ruhnke,¹ Rainer Obenaus,² Ute Kettritz,³ Andreas Kleina,² Günther Morack² and Wolfgang Schneider¹

¹Institute of Pathology, ²Department of Gynaecology and ³Department of Diagnostic Radiology, Berlin-Buch Medical Centre, Berlin, Germany

Long-term survival in patients after breast conserving therapy (BCT) is similar to that after mastectomy. Nevertheless, there is a significant risk of local recurrence. Although local recurrence does not appear to affect the survival, there certainly is associated morbidity and attendant emotional trauma present. The margin status was shown to be a risk factor for local recurrence. Microscopic evaluation of the margins of lumpectomy specimens is the only way to define the extent of the tumour, especially of its intraductal component, and the adequacy of resection. We intended to check the influence of a standardised protocol for pathological examination on the results of histological margin assessment. Moreover, we wanted to investigate the effects of margin status and size of the area of the DCIS-component on the choice of treatment. Between February 1994 and February 1996, 582 women had an unilateral breast excision at the Berlin-Buch Medical Centre. In 233 patients (71.8%) there were no clinical or mammographic contraindications for BCT and their carcinomas were treated by conservative surgery and irradiation. The aim of all tumour excisions was the complete removal of the tumour. As a result of our standardised margin investigation, in 28% of cases there was microscopic evidence of tumour tissue in the margins of 100 consecutive BCT specimens although the margins looked clear macroscopically. In two periods when histological investigations were not carried out on non suspicious-looking margins and the margin assessment was non-standardised, the evidence of tumour could be found in only 2% and 12% of the patients respectively. In each case with invasive carcinoma or DCIS detected in paraffin slides of the margins, either directly at the resection line or within a distance of 5 mm from it, a second operation followed. Finally, 100 women out of the primary BCT group of 323 patients were advised to undergo mastectomy, and thus 132 / 323 (40.8%) patients with malignancies were treated by definitive BCT. The importance of standardised evaluation of BCT specimens is to select patients for re-excision or for treatment with conversion to mastectomy, and thus reduce local recurrence.

Key words: breast cancer; breast conserving therapy; margin investigation; treatment outcome

Introduction

The efficacy of breast conserving therapy (BCT) and mastectomy in breast cancer has been compared in several randomised clinical trials. The long-

term disease free survival in patients treated by BCT is similar to that of patients treated by mastectomy.¹⁻⁷ Nevertheless, long-term survival should not be the only gauge of treatment efficacy. There is a significant risk of local recurrence.⁸⁻¹¹ Although local recurrence does not appear to affect the survival, it is certainly associated with morbidity and attendant emotional trauma.

Ductal carcinoma in situ (DCIS) has implications for breast conserving therapy regardless whether it

Correspondence to: Dr. Decker, Institut fuer Pathologie, Klinikum Berlin-Buch, Karower strasse 11, D-13122 Berlin, Germany.

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is associated with invasive carcinoma or not. DCIS significantly affects local control rates.¹²⁻¹⁵ Microscopic evaluation of the margins of lumpectomy specimens is the only way to define the extent of the tumour, especially of its intraductal component, and the adequacy of resection.^{11,16-20} We intended to check the influence of a standardised protocol for pathological examination on the results of histological margin assessment. Moreover, we wanted to investigate the effects of margin status and the size of DCIS-component area on the choice of treatment.

Materials and methods

Patients

Between February 1994 and February 1996, 582 women had an unilateral breast excision performed at the Berlin-Buch Medical Centre. The malignancy yield in our centre was 55.5% (327/582). In 4 of these 327 malignancies lobular carcinoma *in situ* was diagnosed. Out of the remaining 323 women, 91 (28.2%) underwent primary mastectomy for various reasons. In 233 patients (71.8%) there were no clinical or mammographic contraindications for BCT and their pT i.s.; pT1, and pT2 carcinomas were treated by conservative surgery and irradiation. They had been evaluated by a team of breast surgeons, radiologists and pathologists before they were given the option of breast conserving therapy. 205 (88.0%) of the tumours treated by BCT were invasive (all but 6 invasive lobular carcinomas had an invasive ductal histology). Except for two tumours with diameters of 22 and 24 mm respectively, all the invasive carcinomas were in stage pT1 (mean diameter 13 mm); 28 (12.0%) of the 233 tumours treated by BCT were "pure" DCIS without invasion (pTi.s.).

Surgery

All tumour excisions were performed by the same team of gynaecologists under supervision of an experienced breast surgeon. The aim was complete tumour removal by wide excision with an attempted margin of 10 mm, which would ensure at least 5 mm of macroscopically healthy tissue. In the cases of positive margins on gross inspection or a macroscopic distance less than 5 mm between the tumour and excision margin, the site of the margin involved was re-excised unless an indication for

mastectomy was given. The data for this study have been derived from the primary excision specimens. In every case with invasive carcinoma or DCIS detected in paraffin slides of the margins, either directly at the resection line or within a distance of 5 mm to it, a second operation followed. Taking into consideration the surgical possibilities, re-resection was performed always when the diameter of the DCIS ("pure" or as an component of invasive carcinoma) was less than 40 mm; in all other cases, especially such with DCIS diameters exceeding 40 mm, the patients are advised to undergo mastectomy. In all patients with invasive tumours axillary dissection was performed, which was not done for DCIS.

Pathology protocol

In order to ensure standardization, we base our histopathological investigations of BCT specimens on a practice protocol.²¹ This protocol includes eight steps:

1. Review of the preoperative clinical checklist.
2. Preoperative interdisciplinary consultation with gynaecologists, radiologists and pathologists.
3. Wide excision of the lesion (see above), after mammographic hook wire localisation if necessary.
4. Orientation of the BCT specimen on a drawn form showing the nipple - by the surgeon (additionally, the margins are marked with sutures).
5. Review of the intraoperative clinical checklist.
6. Conducting a gross examination and selecting the tissue for microscopic examination, after specimen radiography with needle localisation, if necessary.
7. Review of the pathological checklist comprising gross examination, microscopic evaluation and diagnoses.
8. Postoperative interdisciplinary consultation.

Handling instructions for gross examination and tissue sampling

1. Determination of specimen dimensions.
2. Marking of the margins with Latex.
3. Serial slicing of the specimen at 4 mm intervals in a plane perpendicular to the mammillar-peripheral axis and, of course, perpendicular to the ductal system.
4. Determination of location, dimension, and configuration of the tumour, and measuring its distance to the margins, determination of location and dis-

tance of the radiographic needle, marking as appropriate.

5. Blocking of any suspicious area of the inner part.

6. Blocking of margins: As the slices are made perpendicular to the mamillar-peripheral axis, it is clear that the mamillar and peripheral slices contain margins which can be seen as a plane and can be submitted *in toto* for blocking. The other four margins are sampled from the edges of the tumour-bearing slices and the neighbouring ones (so-called radial sampling).

Definition of positive margins and measuring of macroscopically invisible tumour

Any tumour in mamillary and peripheral tissue blocks is considered as evidence of positive margin. In radial tissue blocks only the presence of tumour in the definitive margins themselves is taken as evidence of positive margin. The distance to the margins of invasive carcinoma as well as of DCIS were determined by ocular micrometry from the slides for measuring smaller spaces. For larger distances, a combination of direct measuring and estimation by reconstruction, based on the standardised handling protocol, was used.

Evaluation of the sensitivity of the standardised procedure

We compared the results of our standardised margin investigation of 100 cases with the analysis of the margin status of 100 BCT specimens, each from two different time periods with different handling. Before 1989 only margins where tumour tissue was suspected on macroscopic examination were investigated microscopically. From 1989 to 1991, margins were evaluated more systematically, but the evaluations were not standardised and did not consider the orientation of the ductal system.

Results

Margin status

In 28% of cases, tumour tissue was found upon the investigation under the microscope, in the margins of 100 consecutive BCT specimens where the margins looked clear macroscopically. In the periods when histological investigations were not carried out on non suspicious-looking margins and when margin assessment was non-standardised, tumour

could be found in only 2% and 12% respectively. Based on our standardised practice protocol we discovered invasive carcinoma in 8% of cases investigated under the microscope exclusively as invasive carcinoma, 14% of the tumours discovered were only carcinomas *in situ*, and in 5% were combined invasive and intraductal carcinomas.

Therapeutic consequences

Primary in 233 (71.8%) of 323 women with malignancies there were neither clinical nor mammographic contraindications for BCT. DCIS was found much more frequently than invasive carcinoma within a 5 mm distance to the surgical margin or transected at the resection line. There were 144 secondary operations (re-excisions or secondary mastectomies) performed because of the positive margin status or because the extent of the DCIS-area was more than 40 mm. Finally, 100 women out of the primary BCT group of 323 patients were advised to undergo mastectomy, and thus 132/323 (40.8%) patients with malignancies were treated by definitive BCT.

Discussion and conclusions

Initial studies on recurrence rates following wide local excision used a margin of excision of 5 cm, but the cosmetic results were poor.²² Subsequently, the trend has been towards taking less and less tissue. Better cosmetic results has been achieved, but a lumpectomy alone is associated with a high incidence of local recurrence.²³ The hypothesis that recurrence is due to residual tumour is supported by patterns of failure studies.^{10, 24} The margin status is shown to be a risk factor for local recurrence.^{14, 25} Though excision may be clinically adequate, microscopic examination may reveal tumour at the specimen edge,^{1, 25-27} and therefore confirmation of clearance by pathological examination must be sought.

Our results verify a strong influence of our practice protocol on the results of the examination of BCT specimens: Firstly, there is a higher sensitivity for tumour bearing margins compared with random sampling of margin tissue. Moreover, based on the consideration of the ductal orientation, our protocol offers a better chance to detect *in situ* components of tumour in the margins. With our method we are able to define exactly the tumour

bearing margin and thus also the site of re-excision, if necessary.

Finally, based on our protocol, it is possible to determine the size of the area involved by DCIS. The proximity of DCIS to a marked margin is determined by direct measuring and ocular micrometry. Based on the standardised sampling, we estimated the diameter of DCIS by combining direct measuring and reconstruction in a manner similar to that of the Van Nuys group.²⁸ This has got very strong implications for BCT: Recent results by the group of Schnitt et al. have shown that an extensive intraductal component (EIC) as defined by Conolly and Schnitt²⁹ significantly affects local control rates only when the non invasive component contributes to the residual tumour load in the breast.¹⁴ With complete excision for EIC-positive invasive breast carcinomas, irradiation provides a local control rate equal to that of EIC-negative lesions. Therefore EIC *per se* should not be considered a contraindication to BCT unless substantial DCIS remains in the breast.²⁶

The standardised practice protocol for the handling of BCT specimens provides the clinical team with more detailed information about margin status and the size of DCIS component of the tumour than was available before.

The aim of standardised evaluation of BCT specimens is to select patients for a re-excision, or for treatment with conversion to mastectomy. We think that such careful planning of treatment assures better tumour control rates and cosmetic outcome than more aggressive surgery.

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