Review Article

Current controversies in the treatment of ductal carcinoma *in situ* of the breast

Giorgia Garganese[1*], Simona Maria Fragomeni[1*], Sonia Bove[1], Maria Teresa Evangelista[1], Ida Paris[2], Danilo Di Giorgio[1], Daniela Andreina Terribile[1], Riccardo Masetti[1]

[1]Multidisciplinary Breast Center, [2]Division of Gynecologic Oncology, Fondazione Policlinico Universitario Agostino Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy

Contributions: (I) Conception and design: G Garganese, SM Fragomeni, DA Terribile, I Paris, R Masetti; (II) Administrative support: MT Evangelista, S Bove, DD Giorgio; (III) Provision of study materials or patients: SM Fragomeni, MT Evangelista, S Bove, DD Giorgio; (IV) Collection and assembly of data: G Garganese, SM Fragomeni; (V) Data analysis and interpretation: SM Fragomeni, G Garganese, DA Terribile, I Paris, R Masetti; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Simona Maria Fragomeni, MD. Multidisciplinary Breast Center, Fondazione Policlinico Universitario Agostino Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy. Email: simona.fragomeni@gmail.com.

Abstract: Ductal carcinoma in situ (DCIS) represents a disease that includes different risk categories and does not necessarily turn into invasive cancer. The 20% of all newly diagnosed breast cancers consist in DCIS, with an incidence increased due to the widespread diffusion of screening programs. Once upon a time, mastectomy was considered the gold standard in treatment of DCIS, but over the years, breast-conserving surgery (BCS) has been included as the treatment of choice for patients with small lesions. Several randomized trials demonstrated that adjuvant treatment as radiation and ET reduce the risk of local recurrence, including invasive recurrences. Therefore, in patients with DCIS susceptible to conservative surgery, the key decision for management is represented by the addition of radiotherapy (RT) or ET. With the variety of surgical and adjuvant treatment options available, there has been great interest in tailoring therapies to the individual, with the goal of optimizing the balance of risks and benefits. From the observation of the first data showing how such treatments are not clearly associated with an improvement in disease specific mortality, the upcoming hypothesis is to consider omitting some of such treatments or to plan close surveillance for low risk lesions. Prospective studies on women treated with BCS alone have identified low risk lesions. Actually, the main challenge is how to recognize cases that will not progress to invasive lesions. Despite all the studies carried out and the many available data, there are no unique and universally accepted treatment criteria, so some issues of controversy are still open.

Keywords: Ductal carcinoma in situ (DCIS); treatment; breast cancer; review

Submitted Jul 01, 2017. Accepted for publication Aug 15, 2017.
doi: 10.21037/tcr.2017.08.33
View this article at: http://dx.doi.org/10.21037/tcr.2017.08.33

Introduction

The incidence of ductal carcinoma in situ (DCIS) has rapidly increased in recent years both due to the widespread use of screening programs and to the technological improvement of diagnostic methods.

In fact, if in the past the percentage of DCIS was around 1–2% of all breast cancers (1), currently, the incidence is the 20% of all new diagnoses (2).

As well as with invasive cancer, DCIS treatment has undergone many changes over the years. In fact, there has been a shift from considering mastectomy as a primary option to conservative surgery. Similarly, additional treatment options such as radiotherapy (RT) and ET have

been evaluated as reducing the risk of recurrence and included.

Despite the prognosis of this disease is far better compared to invasive breast cancer (IBC), the specific scheme of therapy still remains controversial in several aspects. Many therapeutic options are available for the treatment of DCIS and related to surgery, radiotherapy and medical treatment. Moreover, in the present era, there is an ever increasing tendency towards tailored treatments, balancing the risks and benefits of each option. Therefore, because the available options are so many, there is no univocal conduct and many aspects remain a matter of debate.

Controversies

Screening detection

The wider use of screening programs combined with advances in imaging technology have determined an increased diagnosis of early stage IBC as well as other occasional findings including DCIS (3). In fact, in the last decades an increase of 7.2-fold in DCIS diagnosis was recorded (4).

When DCIS is incidentally diagnosed it is mainly associated to the presence of microcalcifications (5) on digital mammography (MG) and/or tomosynthesis. In the rest of the cases, when radiological signs are missing (up to 40%—mostly low-grade DCIS) it may be unrecognized at screening and often unrelated to symptoms (6). Anyway, since not all DCIS have the potential to evolve in malicious form, the open question remains whether a diagnostic failure could have an impact on the following patients' clinical course.

Are all the screening detected diagnoses useful or not?

Data from two retrospective studies evaluating the outcome in patients with undiagnosed DCIS in a biopsy specimen, showed that 40–50% of cases will evolve in invasive cancer after a time interval of 10–15 years (7). In this studies, in fact, were involved patients treated with biopsy because of a pathologic diagnosis of benign lesion. The same specimens were subsequently evaluated as site of DCIS instead of benign finding, so the authors were able to determine the natural history of DCIS treated with biopsy alone through patients' follow-up.

So, even though the screening is addressed to early invasive cancer diagnosis, it could be also useful to detect that specific portion of DCIS which is intended to evolve in invasive carcinoma; up to date no specific radiological or histological features are available to predict the progression to invasive cancer.

For this reason, the standard care after a DCIS diagnosis currently still include a surgical treatment, combined with possible additional RT and ET. However, there are multiple controversies in all the fields concerning the management, from pre-operative study to adjuvant treatments.

Preoperative imaging

Usually, the radiological methods for preoperative evaluation include: standard MG, digital breast tomosynthesis (DBT), MRI and ultrasound (US) with different level of evidence related to the clinical features of DCIS.

MG *vs.* tomosynthesis

Several studies demonstrates that DBT improves the accuracy of evaluation of DCIS extension, compared to MG. Berger *et al.* in 2016 (8) found that DBT was more precise than MG in tumor size prediction, referring to histology, thanks to the 3D representation of the breast but no benefit was reported in the assessment of multifocality, multicentricity or associated invasive component; moreover the time necessary to read the exam was longer than standard mammogram (9).

Plus MRI or not?

Since DCIS may extend beyond the microcalcification area, a potential role for MRI should include a possible advantage to define tumor extension, the presence of multifocal or contralateral lesions and associated invasive component, on the base of angiogenesis and vascularization (10-19).

This information would be clearly relevant to surgical planning; despite this, no data are available to confirm these benefits that currently remain only potential for DCIS.

In a review on the role of MRI in the assessment of the DCIS tumor size, including 17 studies, dating from 1995 to 2008, the accuracy widely vary from 13–88% (6).

Other studies describe the risk of overestimation of DCIS extension: Pilewskie *et al.* reported a more frequent failure of DCIS detection on MRI compared to MG (20/217 or 9.3% compared with 8/352 or 2.3%, P=0.0001); but when detected (if more than 1 cm), a more frequent size overestimation was reported on MRI (43.9% of cases *vs.* 34.7% of mammogram, P=0.06); conversely, MRI was able to detect more frequently the multifocal component

(25.7% *vs.* 15.3%, P=0.0001) and bilateral abnormalities (25.7% *vs.* 6.5%, P=0.0001) (20). More breast conserving surgeries were reported in patients who underwent standard preoperative imaging, with a larger proportion of appropriate surgical choice (P=0.06), while a greater rate of mastectomy was reported when a preoperative MRI was performed (34.6% *vs.* 27.4%, P=0.20) (20).

Chung *et al.* studied the impact of MRI on the surgical treatment planning, finding a management change in 26% of patients, of which 15% was considered as appropriate and 11% unnecessary (21).

More other studies examined the effects of pre-operative MRI on surgical management in patients with DCIS, finding mixed results on the increase of the mastectomy rate (22-24).

Finally, several studies showed an advantage from MRI in the detection of contralateral lesion which is, yet, in a low percentage (3–4% of MRI-detected synchronous contralateral breast cancers) (21).

US what role?

Some US findings have been identified as useful in the DCIS detection, including masses, ductal abnormalities, hyperechoic spots and structural distortion (25). In particular, DCIS has recently been described as mainly associated with non-mass lesions in approximately 60% of cases (25-28).

Considering the only rate of DCIS not associated with microcalcifications, Su *et al.* found a significant benefit in the use of US compared with DBT and digital mammogram, reporting a detection rate respectively of 95%, 84% and 68.4% and a diagnostic accuracy of 66%, 68.4%, and 43.9%. These results are confirmed in case of dense breasts with non-calcified DCIS (81.2%, 63.8%, and 95.0%) (29).

In summary, compared with other diagnostic tests, ultrasonography remains dependent on the operator's experience and device quality and does not allow a reproducible record of the detected findings; however, in the case of unrecognized invasive component, some theoretical advantages include the opportunity to identify breast solid masses or lymph node involvement and to perform a US guided biopsy.

Surgical treatment

Surgical treatment is often affected by the efforts to identify the correct extension of DCIS, preoperatively and intraoperatively. Indeed, histological reports show incomplete resections and margin involvement more frequently in DCIS surgery than for infiltrating tumors (3,30). In 2012, van der Heiden-van der Loo and colleagues published the data collected on the histological outcome of surgical margins after breast-conserving surgery (BCS). From the examination of DCIS cases emerged a percentage of margins described as positive (focally or more than focally) of 27% *vs.* 9.1% for invasive carcinomas (30). Moreover, including in the research both positive and close margins for DCIS, data on surgical treatment available in literature report an overall percentage, between 48% and 59% (31). Generally, these patients receive the indication of a second surgery for the excision of the involved margins.

One way to reduce the magnitude of the problem should be to perform a precise preoperative location and intraoperative margin evaluation.

Tools for preoperative localization

The different means for preoperative localization are mainly delivered under MG guide, the standard of reference, and sometimes under US guide. Many novel techniques can be applied, such as the ^{99}Tc radioguided occult lesion localization (ROLL) and the radioactive ^{125}I seed implants, as well as some standard techniques, like the wire localization (WL) or the release of a titan clip during core biopsy procedures.

The stereotactic localization is more difficult in case of extensive disease: multiple wires or different markers need to be place to define the boundaries of the lesion (32). In this regard, a prospective randomized study concluded that the use of multiple wires or multiple radiotracer injections is highly recommended in the case of microcalcifications extended more than 3.5 cm, to obtain a higher complete surgical excision rate (33).

However, data on radioguided methods are still conflicting. In fact, if on one hand the radiotracer is poorly visible on mammogram and therefore a precise preoperative mapping of extended lesions could be difficult using the ROLL technique, on the other hand many different studies show how WL is associated to more frequent positive margins. Instead, Luiten *et al.* showed encouraging data, achieving a complete DCIS resection in the 82% of patients undergoing radioactive seed localization (RSL) compared with 74% marked with WL (P=0.139) (3).

Furthermore, Lovrics *et al.* also found that RSL required shorter operative time and was easier to perform compared with WL, being more precise to estimate the exact position,

distance, and direction of the lesion (34).

Finally, a Cochrane review published in 2015 concluded that ROLL and RSL were equally reliable compared with WL, but since more data are still available on the WL, it is currently still considered the standard of reference (35).

Intraoperative detection and margins evaluation

Intraoperative margin evaluation could be useful to reduce frequency of positive margins and delayed surgical re-excisions, after pathology exam.

Even if currently there is no standard scheme for intraoperative margins assessment (36), one of the most frequently used technique is the intraoperative specimen radiogram, which verify the removal of suspicious calcification and guide a possible intraoperative re-excision; this technique is currently recommended by some organizations as the German Working Group of Gynecologic Oncology (AGO) (37-39).

Nevertheless, up to 44% of cases with radiologic negative margins can reveal positive histologic margins (40).

In order to overcome this limit, several systems have been investigated to correlate the sample X-ray to pathological report, using gridlines (41) or performing serial radiograms of consecutive slices (36,42-44). Ciccarelli and colleagues (37) demonstrated that more accurate margin assessment might be achievable by two orthogonal views.

Sample radiogram appears to be extremely accurate in determining whether or not a lesion has been excised (36,45). Some authors have studied the value of radiological margin of 10 mm that was found to be associated with a mean histological margin of 4 mm, with a sensitivity of 64% (36,45).

The role of frozen section remains unclear due to several limitations (46) even if there are some published data with encouraging results (44,47-49). However, none of the reported systems resulted superior if compared to the others and the definition of radiological negative margin remains today a challenge.

Sentinel node biopsy (SNB) or not?

The main international societies, as NCCN and ASCO, do not recommend axillary lymph node evaluation for patients undergoing BCS since a non-invasive carcinoma cannot determine lymph node metastasis; instead, an SNB may be needed in patients undergoing total mastectomy (TM), as well as in case of surgery performed in anatomic sites that compromise a future procedure (central breast, upper outer quadrant, or axillary tail) and in case of large volume DCIS (50,51).

Despite these recommendations, a retrospective review conducted on cases of DCIS treated with BCS in the Netherlands between 1998 and 2011, showed a rate of axillary surgical procedures of 43.9% (including a 4.5% of axillary lymph node dissection) (52).

Findings from a series of 232 DCIS patients undergone SNB, registered on the Helsinki sentinel node database, showing a positive node in 6% of cases (only 1 macrometastasis, 1 micrometastasis and 12 ITC) open another important issue (53).

According to some theories, a positive sentinel node could be explained as a result of a diagnostic maneuver (core biopsy or surgical biopsy) which would produce a passive dislocation of epithelial cells: an open discussion is ongoing on the prognostic value of this metastasis and if we can consider them as true metastasis.

Moreover, a rate of identified DCIS-associated invasive component has been reported in 10% to 20% of excision specimens (51). A possible explanation of a positive SN in a pure DCIS would be the presence of an associated unrecognized invasive component, which could have been removed during a preoperative diagnostic maneuver or missed to an incomplete sampling of the resected tissue. Therefore, in the light of several studies which found an invasive focus after further samples sectioning, it has been widely shared that an extensive mapping of the DCIS samples is required and strongly recommended (54).

Surgical treatment and resection margins

Mastectomy was considered for long time the standard treatment in case of DCIS. To date, BCS with or without RT, is considered to be the optimal treatment and equivalent to mastectomy in terms of overall survival; but actually around 30% of patients with DCIS still undergo mastectomy (55-57).

What is debated is the optimal surgical margins in order to avoid local relapse. Currently, local relapse is described as an event in approximately 20–30% after BCS, and in 10–15% if RT is added. The main concern related to relapse is that around 50% of them are invasive diseases with different prognosis compared to DCIS recurrences (58). Therefore, having free surgical margins is a key point. MacDonald *et al.* showed how patients with a margin positive for DCIS had a risk of recurrence 7.7 times greater than those with a

10 mm disease-free margin width (59,60). In addition, a meta-analysis of randomized trials conducted on DCIS cases was published in 2010. In this work of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) it emerged that patients with positive margins have a double risk of ipsilateral recurrence (IR) compared to those with negative margins. Although radiation was included in the treatment, the 10 years IR for these patients was 24% *vs.* 12% in case of negative margins (61). Because of this risk, a rate of surgical re-excision margins is described in literature from 20% to 70% (62-67). To avoid re-surgery, some authors suggest to take additional tissue from the cavity, removing a greater portion of breast tissue or to study intraoperatively the surgical margins through X-ray, with less breast tissue removed as reported (reduction of tissue volume approximately of 40–50%) (68).

Another issue is the definition of free surgical margin on which not all the international organizations actually agree. NICE guidelines recommend a minimum 2 mm margin for DCIS (69). At the British Association of Surgical Oncologists (BASO) meeting in 2009, the Association of Breast Surgeons (ABS) recommended as an acceptable clear margin more than 1 mm (70). Moreover, in case of DCIS is not possible to consider the limit of no ink on tumor, as it is potentially related to increased recurrence rates. So, SSO/ASTRO/ASCO guidelines recommend, as optimal in DCIS, a free margin of 2 mm in case of BCS and RT (71).

A further unsolved question is represented by the nature of DCIS which may frequently have a discontinuous growth pattern; usually gaps less than 5 mm in diameter are described in 85% of cases (72,73); that increase the risk of residual disease and the rate of relapse, since a 2 mm free margin resection could fall within a 5 mm gap and cause an unrecognized disease persistence. Therefore, identifying the predicting factors for disease persistence is absolutely useful. Data obtained from the analysis of multiple studies reveal some risk factors for positive margins: (I) a size greater than 2.5 cm (74-76); (II) high grade DCIS (74,75); (III) MG size underestimation more than 1cm compared to pathology (75); (IV) clinical presentation without calcifications or very dense breasts (77); (V) micropapillary DCIS (78).

Finally, there is general agreement on mandatory re-excision in case of transected margin, which implies a potential incomplete resection and that 'no ink on tumor' is not applicable to DCIS. Moreover, in case of multifocal disease, not even the negative margin is able to ensure the absence of further DCIS foci in the remaining breast tissue.

What remains controversial is if a negative margin >2 mm can further reduce the risk of recurrence, potentially having an impact on adjuvant treatment as radiation therapy. Actually this is not supported by evidence.

The last unsolved issue regards a margin width less than 2 mm. Both the NSABP DCIS trials, which required a margin of no ink on tumor (79) and the study of Van Zee *et al.*, highlighted the absence of difference in terms of recurrence risk between negative margins of 2 mm and negative margins with size greater than 2 mm (80). What remains unclear is how the addition of RT can resize the role of margin width on local recurrence.

Finally, some technical issues that limit the actual evaluation of margins cannot be yet overcome, such as tissue flattening when the specimen loses the surrounding support, modifying the true surgical margin; the slipping of the superficial ink into the tissue depth; the bias due to the assessment of tumor distance from ink in a single section that cannot be representative of the entire lesion.

Avoid surgical treatment could become an option?

Upcoming studies are evaluating if a low risk disease could not be treated at all and addressed to surveillance. One of the most relevant ongoing studies is the LOw Risk Dcis (LORD) study, carried out by European Organization for Research and Treatment of Cancer (EORTC) and the Dutch Breast Cancer Research Group (BOOG). This is a phase III randomized trial, which involved different international centers. The primary objective is to assess if a strict surveillance for patients diagnosed with a low risk DCIS can be considered safe and non-inferior compared to standard treatment (local excision, local excision and RT, mastectomy and/or endocrine treatment). Patients included in the study are women older than 45 years affected by low grade DCIS with microcalcifications, non-associated mass, diagnosed by screening or occasional MG, American Society of Anaesthesiologists (ASA) score of 1–2 and life expectation longer than 5 years. The outcome measure will be the rate of patients without invasive ipsilateral breast cancer (assessed at 10 years) (81).

Another European randomized prospective ongoing trial, the surgery versus active monitoring for low-risk dcis (LORIS) is studying the difference in terms of safety between observation *vs.* standard surgical excision in women with low or intermediate grade DCIS. The study primary outcome is the difference at 5 years of disease free survival (measured as invasive breast cancer events). The inclusion

criteria provide patients fit for surgery, older than 46 years, DCIS described as non high grade at pathology report, and microcalcifications identified when asymptomatic (82).

Both of these studies will provide useful data for the purpose to modify therapeutic behavior in a specific subclass of low-risk patients.

Risk assessment for local recurrence

Although risk factors as age, tumor diameter, grading and the margin status are clearly defined in several studies, many efforts have been made to create a score that would quantify the risk of local (*in situ* or infiltrating) recurrence tailored to the specific risk of the single patient. Nevertheless, there is no agreement on the reference standard for risk assessment in DCIS.

The Van Nuys prognosis index (VNPI), was first described in 1996 (83), and since then it was found to be a useful tool in treatment planning. This is a prognostic index based on the evaluation of four factors (tumor size, tumor-to-margin distance, grading and comedonecrosis). The final score was originally composed by the sum of pathologic classification score + margin score + size score. Secondly, the University of Southern California (USC) added a fourth factor, patient age, that has been described in many works as a clinically relevant parameter in predicting local recurrence after BCS for DCIS. In fact, an analysis of local recurrence rates stratified by age and conducted at USC showed how there is a risk change at age 40 and 60. Therefore, the final formula for the USC/Van Nuys prognostic index became pathologic classification score + margin score + size score + age score (84). This score is linked to specific decision treatment options, related to the different results: from 4 to 6 (30% of total diagnosed DCIS), excision may be suggested while surgery plus radiation needs to be provided in case of scores between 7 and 9 and, finally, mastectomy needs to be considered in scores 10–12. Clearly, all these options coming from the USC/VNPI are, at present, a guideline for counseling with the patient.

Sometimes the re-excision allow the surgeon to change the score, down-scoring the disease or, conversely, up-scoring the tumor (i.e., larger tumor size, a higher nuclear grade). It is interesting that with a high score, even with radiation therapy, the local failure rate may be quite substantial. The limits of this classification include the specific pathologic assessment of specimens with the lack of external validation of the method and data that didn't come from a randomized trial (85).

Recently, at Memorial Sloan Kettering Cancer Center was developed a multivariable nomogram for the estimation of local recurrence risk. This nomogram has been created for patients with DCIS submitted to BCS and evaluates the risk of local relapse at 5 and 10 years (85). Even in this case there are several limitations due to the use of retrospective data outside the context of a randomized trial (85).

Finally, in the era of the expansion of multi gene expression profiling techniques, Solin and colleagues in 2013 created a specific panel for DCIS that includes 12 genes (7 cancer related and 5 reference genes), the DCIS Oncotype Dx (86).

The study was conducted on the same population of the ECOG E5194 study, a prospective trial on low-risk patients subjected to surgical excision without radiation.

From this study emerged that DCIS with low/intermediate grade and T less than 2.5 cm or high grade DCIS associated with T less than 1cm showed respectively, a 14.9% and 19% risk of local recurrence at 10 years. A possible explanation is that there are other criteria, different from pathology, that can determine the different risk category (low-intermediate-high). With the DCIS Oncotype Dx Score the 10 years risk is expressed as a continuous variable related to confidence intervals.

An interesting data is that this score, when low, gives more accurate rates in predicting the risk of local relapse while, greater DCIS scores are associated with a risk higher than double, generally in case of intermediate/high grade disease.

Adjuvant treatment

ET

Even if, available data suggest that endocrine adjuvant therapy provides a recurrence risk reduction in ipsilateral breast after BCS and for contralateral breast, no data have shown any advantage in terms of survival.

Moreover, ET is not free of side effects; therefore currently the indication needs to be evaluated on the basis of individual risk factors. That's why in clinical practice patients affected by ER positive DCIS tumors need to receive counseling before starting this treatment. Specifically, two randomized phase III clinical trials demonstrated that adding tamoxifen reduces the risk of ipsilateral and contralateral breast cancer events by approximately 30% at 10 and 15 years (79,87). In the UK/ANZ DCIS study tamoxifen reduced the incidence of all

new breast events (both ipsilateral DCIS and contralateral tumors), without effects on ipsilateral invasive disease (87). The second trial is the NSABP B-24, a double-blinded, placebo-controlled trial. All patients enrolled affected by DCIS and treated with BCS were randomly assigned to RT or RT plus tamoxifen (88). Both the treatment arms were homogeneous for risk factors distribution and statistically well balanced. The results of this trial showed that RT + tamoxifen reduced by 32% the incidence of IBTR compared with RT alone (6.6% *vs.* 9.0%), with a 15-year IBTR cumulative incidence of 10.0% for RT and 8.5% for RT + tamoxifen.

Another question was the effect of aromatase inhibitors in this patients subset. Two phase III trials were published on this topic (89,90). The IBIS-II (DCIS) trial, is a double-blind, randomized placebo-controlled trial, in which postmenopausal patients treated with BCS plus or not RT were randomly assigned to receive anastrozole or tamoxifen for 5 years. No statistically significant difference in overall recurrence was observed between the arms as similar was the number of adverse events reported; more fractures and strokes with anastrozole and more gynecological cancers and thrombosis with tamoxifen (89).

The NSABP B-35 trial, on postmenopausal women with hormone-receptor positive DCIS treated by BCS + RT, provided a randomization between tamoxifen and anastrozole for 5 years. In this study no clear differences were registered overall, with a little benefit of tamoxifen in patients younger than 60 years (90). As in the IBIS II trial, the Authors observed greater incidence of uterine cancer not statistically significant.

Finally, we can affirm that there is substantial agreement on the role of tamoxifen improving outcome in premenopausal patients and that is possible to consider an aromatase inhibitor in postmenopausal patients or in case of side effects due to tamoxifen. To reduce these effects, some authors suggested a tamoxifen reduction of dose from 20 to 5 mg/d (91). Data on this studies need to be confirmed by randomized trials.

RT

The effect of RT after conservative surgery in DCIS on reducing local recurrence rate was demonstrated in many randomized trials. At least in four of them, National Surgical Adjuvant Breast and Bowel Project-B17 (NSABP-B17), European Organisation for Research and Treatment of Cancer 10853 (EORTC 10853), the United Kingdom, Australia, and New Zealand trial (UKAusNZ), and the Swedish (SweDCIS) trial a 50% reduction in IR risk was observed when patients were randomly assigned to conservative surgery plus RT (79,87,92-99). Also the meta-analysis from the Early Breast Cancer Trialists' Collaborative Group showed that 10-year local recurrence was reduced from 28.1% after lumpectomy alone to 12.9% with RT (P<0.00001) (61). To date, none of these trials was able to demonstrate an effect on distant metastases and survival. In particular, in all these studies was evaluated the role of whole breast RT, which showed overall positive results. However, it remains controversial whether RT may show a different role in specific patient subsets or whether different treatment methods can be applied.

Additional benefits from boost?

Controlled randomized trials have demonstrated that, in case of IBC, the addition of a RT boost directed to the tumor bed may further reduce the risk of IR (95-97). Actually multiple prospective trials as BONBIS and BIG 3-07/TROG 07.0111 are still ongoing for evaluation of patients' follow up to demonstrate if RT boost my play the same role in case of DCIS (99). Moran *et al.* in 2017 published their results from a multi-institutional database including 4,131 patients. The use of RT boost was associated with reduced IBTR on univariate and multivariate analysis at 10 and 15 years. Related to margin status, in this study the boost remains beneficial in case of negative margins but no significant statistical difference was highlighted when margin status was stratified using the SSO/ASTRO/ASCO definition (negative >2 mm). Despite that, in the paper, the authors described an estimated absolute benefit of 3.6% at 15 years, comparable to the benefit for a boost in invasive cancer as showed in the EORTC 22881 trial (4.4% at 20 years) (100).

Therefore, in conclusion, the role of boost in positive margins remains not determined.

For patients with a life expectancy more than 10–15 years and negative margins the association of boost and whole breast radiation (WBR) needs to be considered. Data from randomized controlled trials will clarify fields of application of this technique. If close margins, defined as less than 2 mm but not infiltrated, may have a benefit from addiction of boost remains controversial.

A role for accelerated partial breast irradiation (APBI)?

APBI is a form of localized RT delivered on the tumor bed after surgery, which has been far investigated in many

clinical trials over the last years. Many different schedules, delivery systems and time settings have been proposed as an alternative to the conventional whole breast irradiation (WBI); unfortunately, overall results were controversial and mostly less favorable than standard therapy, in terms of IBTR and cosmetic outcomes (101).

In the mess of the heterogeneous studies investigating APBI, only one proves conclusively that adjuvant APBI is as effective as conventional WBI: the randomized, phase 3, non-inferiority trial, published in 2016 by the Groupe Européen de Curie thérapie of European Society for RT and Oncology (GEC ESTRO), in which a post-operative multicatheter brachy-therapy was delivered in carefully selected patients with early breast cancer and pure DCIS (102).

In this study, the DCIS patients were included according to the GEC ESTRO eligibility criteria previously established in 2009 (103), but numerically they represented only a very minority in both the groups compared (4% in APBI arm and 6% in WBRT). Thereafter, APBI with multicatheter brachytherapy should be currently considered as a feasible and safe option for low risk breast cancer patients (104), providing many advantages, such as shorter course (3–5 days compared to 5–7 weeks in WBI) and less logistical problems for women who live far away from RT centers, though requiring a precise timing for post-operative insertion of the interstitial catheters and a necessary close team collaboration between well trained and skilled specialists including surgeons, pathologists and radiation oncologists.

Despite this, detailed criteria to address patients to one treatment or to the other are not still clarified and need to be yet discussed and shared.

Conclusions

DCIS treatment needs to be planned on the basis of patients characteristics as age, clinicopathologic features, tumor biology, life expectancy and patient's preference. In fact, an optimal approach includes an accurate counseling and discussion with patients to examine the different treatment options with pros and cons of each of them. We are still waiting for data from the ongoing clinical trials to consider an active surveillance instead of surgical treatment and to clarify the true necessity of RT and ET after breast conserving surgery. Therefore, in view of the currently available data, outside of a clinical trial, surgical treatment remains the standard treatment until more risk stratification tools will become available.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research* for the series "Update of Current Evidences in Breast Cancer Multidisciplinary Management". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.08.33). The series "Update of Current Evidences in Breast Cancer Multidisciplinary Management" was commissioned by the editorial office without any funding or sponsorship. RM served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Garganese G, Fragomeni SM, Bove S, Evangelista MT, Paris I, Di Giorgio D, Terribile DA, Masetti R. Current controversies in the treatment of ductal carcinoma *in situ* of the breast. Transl Cancer Res 2018;7(Suppl 3):S307-S318. doi: 10.21037/tcr.2017.08.33

