DUCTAL CARCINOMA IN SITU (DCIS): WHAT NOW?
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It is not common to see a case of pure DCIS in the public health sector of South
Africa. The diagnosis is typically made in the context of a palpable lesion, of
symptomatic disease or of opportunistic screening. On the other hand, DCIS is
frequently encountered when operating on an invasive index lesion. Most invasive
cancers still carry a variably sized component of this pre-invasive pre-cursor lesion¹.

The DCIS component, non-palpable and invisible to the surgeon, often unsuspected
on pre-op imaging, is only detected on histology and may be responsible for close or
involved margins after surgery. The multidisciplinary meeting must then make the
decision: re-excision or radiotherapy?

In the developed world and the health insured part of the South African population
where population based screening programmes have been introduced is very
different. Over the last 30 years the incidence of new DCIS cases is reaching
epidemic proportions. More than one fifth of the new so-called “cancer” cases are
histologically DCIS of various grades².

DCIS is also referred to as stage 0 breast cancer and is included in American breast
cancer statistics. This is debatable since it is actually a non-obligatory precursor. The
incidence in the US increased from 2/100000 in 1975 to 30/100000 by 2005³
reflecting the advent of mammography.

THE DILEMMA
The so-called “dilemma of DCIS” refers to the uncertainty about the natural history.
DCIS can be considered a malignant lesion that has a favorable prognosis and that
requires aggressive treatment to minimise future cancer events.
After the paradigm shift from mastectomy to breast conserving surgery (BCT) for invasive breast cancer, for nearly a decade the standard treatment for DCIS, the precursor, paradoxically remained mastectomy. Only following the publication of several trials in the 1990s that showed the safety of breast-conserving surgery was this accepted as a standard of care. Mastectomy is considered overtreatment for a condition that carries a very low mortality rate unless there is extensive disease.

The prescribed treatment is mastectomy, or lumpectomy and radiotherapy. An alternative view sees DCIS purely as a marker of increased risk of developing invasive carcinoma. A lumpectomy serves to exclude the presence of an invasive component (which is found in 20% of cases!), followed by observation or by risk reducing hormonal intervention. Although the estimated progression rate from DCIS to invasive cancer is only 20-30% an initial surgical excision still remains mandatory practice.

The current NCCN guidelines (version1.2016) offer various options for the primary treatment of DCIS:

- Wide local excision (WLE) and radiotherapy (DXT).
- Total mastectomy, +/- Sentinel Node Dissection (SLND), +/- reconstruction.
- WLE without SLND and without DXT for low risk lesions.
- Additional risk reduction endocrine treatment with Tamoxifen or Aromatase inhibitor can be considered for five years, especially for ER-positive lesions.
- Surgical margins are deemed inadequate if less than 1mm and negative if above 10mm. From 1-10mm an indirect correlation with local recurrence rates is assumed.

The treatment decision needs to be based on the prognostic risk stratification, provider’s preference and patient’s choice.
PATHOLOGY

There is no generally accepted pathological classification system. Most often a three-tier system is used dividing DCIS into well, intermediate and poorly differentiated subtypes. According to a consensus meeting from 1997 the pathology report is expected to consist of a description of the morphology (comedo, cribriform, papillary, micropapillary and solid subtypes), more importantly the grade in reference to the nuclear grade (low, intermediate and high), and the presence or absence of comedo or non-comedo type of necrosis. DCIS displays a mostly unicentric, segmental growth pattern and is truly multicentric only in 10% of cases.

It is possible to perform intrinsic molecular subtyping. The HER2 enriched group is comparatively found more frequently than in invasive cancer, the basal-like group less so. The clinical relevance of this observation remains unclear. ER/PR testing however is recommended as routine practice and is required before considering hormonal treatment options.

The recent “B-Path-Study” highlighted the well-known problem of inter-observer variability between pathologists in the diagnosis of DCIS, particularly when distinguishing between low grade DCIS and atypical ductal hyperplasia. The overall concordance rate between the gold standard set by an expert panel and the individual pathologists was 84%, the concordance rate in diagnosing atypia was a mere 48%.

Clinical and pathological factors consistently linked to poor prognosis are: young age below 40 years, high nuclear grade, comedo-type of necrosis, large size of the tumour, close or positive (<1mm) margins, ER negativity and –possibly- HER2 positivity.

SCORING SYSTEMS

The University of Southern California/ Van Nuys Prognostic Index (VNPI) has empirically linked the pathology features of the excised specimen to a management recommendation. Although not universally accepted due to issues of validation and reproducibility the time-honored VNPI remains a widely applied tool that assists in clinical decision-making.
The index has since undergone repeated modifications and was last “fine-tuned” in 2010. It consists of 4 criteria that carry a score of 1-3 each. The resulting score ranges from 4-12/12 (Table 1). Following the algorithm helps to achieve 12 years total local recurrence rates of less then 20%, even for the highest scores (table 2)\(^8,9\). This includes both new DCIS and invasive events. Great attention is given to the integrity of surgical margins and to dedicated whole specimen pathology.

Alternative, although less well established prognostic and management tools include the 10-point Memorial Sloan Kettering Breast Cancer Nomogram, designed to predict the 5 and 10 years recurrence rate\(^10\) and increasingly, the commercial Oncotype DX DCIS score.

It was developed from the Oncotype DX multigene assay for invasive lesions and measures the expression of seven genes, but it is still limited in its evaluation. It has been argued that the transition to invasiveness is not only determined by the genetics of the tumour cells but that there is a critical regulatory role played by adjacent stromal cells\(^11\). Gene assays should only be used as an adjunct to clinical risk assessment.
At least a partial concordance between the above mentioned three scoring systems has been observed, mainly in the low risk group\textsuperscript{12}.

**BREAST CONSERVATION, RADIOTHERAPY AND RECURRENCE**

Since cancer specific survival rates for DCIS were consistently found to be very high (in excess of 95% at 10 years) the measured endpoint to evaluate the benefit of adjuvant radiotherapy is the effect on the local recurrence rates after BCS. There is evidence to prove that adjuvant radiotherapy leads to a relative reduction in ipsilateral recurrence rates of more than 50%.

A meta-analysis of four randomised trials quantified the overall effect with a reduction from 28% to 13% at 10 years of follow up. A similar effect was observed stratified overall risk groups, including the lowest risk group\textsuperscript{13}. No associated survival benefit could be shown.

The use of Radiotherapy (RT) comes with its own cost of short and long-term morbidity, but data are scarce. Even with modern techniques the cardiac dose still ranges from one to five Grey. It was estimated that radiotherapy to the heart results in a linear increase in the rate of major coronary events of 7.4%/Grey\textsuperscript{14}. Once the dose has been given adjuvant RT cannot be repeated. A woman who had DXT for DCIS is precluded from more BCS if she later develops an invasive recurrence. Not surprisingly over many years there have been efforts to identify those patients who can safely omit RT.

The use of radiotherapy in low risk DCIS has persistently been challenged based on the low absolute benefit, not the relative risk reduction. Multiple studies looked prospectively at the feasibility of omitting RT for low-risk patients. The ECOG 5194 began its enrolment in 1997. The initial results were promising, but the recurrence rates reached no plateau and new events followed long after the five years goal line\textsuperscript{15}. Approximately 50% of local recurrence is found to another DCIS, the other 50% is invasive breast cancer. In our current understanding of tumor genetics low risk DCIS will preferentially progress to low risk invasive tumors, while high risk DCIS is inked to high risk invasive cancer \textsuperscript{6}.
Margin status has been a contentious topic since Bernie Fisher’s dictum that “one cell” was enough. It has been agreed that 2-3mm (more recently: 1mm) is acceptable, provided that adjuvant RT is administered. However, in view of the current concern about overtreatment for low risk DCIS lesions the margin issue has been re-examined. It was argued that margins of more than 10mm, irrespective of other risk factors could have a similar effect on the recurrence risk as DXT 16.

WHAT’S NEW?
There is substantial new evidence to a debate that has lasted for decades. Ironically, it seems to support both sides of the controversy. For the first time, with the help of strongly powered observational studies, a very discrete absolute survival benefit of DXT after BCS could be demonstrated – at least in the highest risk groups. Strong risk factors are age below 35, black ethnicity and large tumours.

Clearly, DCIS carries a substantial risk of long-term recurrences. Large SEER based observational studies show recurrence curves that are steadily climbing over a prolonged period of observation. Combining radiotherapy and hormonal treatment after BCS leads to sustained and added benefit17. However, in absolute numbers breast cancer specific mortality rates remain very low.

The following landmark papers have fuelled further debate:

- Worni, 2015: Trends in treatment pattern from an analysis of from SEER data over 20 years. The figure below documents some significant changes in surgical practice since 19905. Of interest: In a sub-analysis of the age group above 70 years 40% of all deaths were from cardiovascular disease, compared to 5% from breast cancer5.

Figure 1. Trends in treatment
• Wallis, 2012: A 15 years follow up of screen-detected DCIS cases (n=700) in the UK found that the cumulative proportion of developing recurrence after BCS at 180 months was twice as high as at 60 months. The authors conclude that the “cure model” as applied for invasive BC is not applicable to DCIS and that a standard follow up of five years will miss a lot of late events.

• Stuart, 2015: A meta-analysis of prospective and retrospective studies with a follow up > 10yrs found that for patients undergoing BCS invasive local recurrence was significantly lower when two rather than one adjuvant treatment modalities were added, ie. RT and Tamoxifen. But there was no significant difference in overall survival.

• Narod, 2015: An analysis of SEER data, 108 196 cases of DCIS from 1988 to 2011, showed an overall 3.3% rate of breast cancer specific mortality rate at 20yrs. Radiotherapy reduced the risk of ipsi-lateral recurrence after BCS from 4.9 to 2.5% at 10yrs but not the breast cancer specific mortality rate. Risk factors for death were young age and black ethnicity.

• McCormick, 2015. RTOG 9804, the first prospective randomised trial compared BCS in good risk group of DCIS against BCS and DXT at a median follow up of seven years. The local failure rate in the DXT arm was 0.9% versus 6.7% in the observation arm. The 15-20 year follow up outcomes are awaited.

• Sagara, 2015: This is a provocative analysis of SEER data from 1988 to 2011. 98% had surgery and 2% did not (N=1169) – for various reasons. While there was an obvious benefit of surgery in the high and intermediate grade DCIS, no significant survival benefit was found for low-grade lesions. Could these be indolent lesions with a low growth pattern?

• Sagara, 2016: In this analysis of SEER data from 1988-2007, 2 groups are compared 1) BCS alone and 2) BCS with DXT. DXT lead to significantly improved survival only in the sub-groups with a high prognostic score, indicating a higher nuclear grade, younger age and a larger tumour size. It was suggested that DXT only be given in those groups that show clear benefit. A prognostic score of 1-6 was found to be helpful.
LESS TREATMENT?
The biological behavior of low-grade lesion, in the non-high risk groups might possibly be following a distinctly benign clinical course and over-treatment is thus a real concern. A review of autopsy studies showed a median prevalence for DCIS of 8.9% (per breast!) in previously undiagnosed women\textsuperscript{22}. This begs the question – could some of the low grade, low risk lesions be altogether moved from the curative into a prophylactic paradigm? \textsuperscript{2} Surgery would be reserved for diagnosis confirmation, exclusion of the presence of an invasive component or it could even be postponed or omitted.

A watchful waiting approach is well established in the treatment of favorable prostate cancers however the public opinion, the media and patients’ activists play an important role. Sagara’s epidemiology data made New York Times headlines on August 20, 2015: “Doubt is raised over Value of Surgery for breast lesion at earliest stage”. Patients are encouraged to make their own choices and understandably they find it very difficult to make an informed decision.

The use of language is critical at this point. The emotionally charged word “cancer” has been challenged, as it profoundly impacts on the patient’s autonomy. It was shown that women with DCIS self-assess their prognosis identically to those with invasive breast cancer\textsuperscript{23}.

When the identical situation and prognosis was communicated by the physician using the three alternative terms: “cancer”, “lesion” or “abnormal cells” a measurable impact on patients’ treatment preferences could be demonstrated\textsuperscript{24}.

Attempts to change terminology date back to 2003 when the WHO proposed the DIN (ductal epithelial neoplasm) classification, this was however never widely adopted. Recently Laura Essermann has introduced the more re-assuring term “Indolent Lesions of Epithelial Origin” (IDLE)\textsuperscript{25}.

Although still experimental, the conservative approach has gained momentum.
Three major prospective randomised trials are recruiting at the moment: the UK based Loris (active surveillance for low/intermediate grade DCIS), the European EORTC-LORD (active surveillance strategy versus conventional treatment) and the US Comet Trial (Comparison of Operative versus Medical Endocrine Therapy for Low Risk DCIS)\(^5\).

**CONCLUSION**
The current discussion revolves around the over- and under-treatment of DCIS. Despite the publication of long-term outcome data from observational and interventional research, the controversy is still far from resolved. Local recurrence rates after BCS are high and the breast cancer mortality is very low.

Can adjuvant modalities be justified for all BCS? Aggressive adjuvant treatment carries its own morbidity, mortality and financial costs. A more robust risk stratification system is needed to assist in decision-making. In the low risk group the role of less or no treatment is currently being studied but it is too early for prime time.

From a South African perspective an overtreatment of “IDLE” lesions is of little concern, as it is limited to a few patches in the private sector that are fed by intensive screening activities. Patients presenting with DCIS in the public sector are at no apparent risk of being over treated, as they are likely to show high-risk features: black ethnicity, large, palpable or symptomatic lesions, features of comedo-necrosis and young age. For the day-to-day management the Van Nuys Prognostic Index remains a pragmatic tool.
REFERENCES


