SOUTH AFRICAN SOCIETY OF CLINICAL AND RADIATION ONCOLOGY

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SASCRO Statement on:
Re: Intra-operative Radiotherapy (IORT) after lumpectomy for breast cancers

The aim of lumpectomy and post-operative irradiation for selected patient with early breast cancer is preservation of the breast while ensuring no increase in the local recurrence rate compared with total mastectomy.

Post-operative external beam irradiation is widely available within South Africa. Kilovoltage IORT is being promoted at select centres.

The SASCRO Committee considers that further evidence is required before IORT can be recommended for routine use outside of a clinical trial.

The evidence for kilovoltage IORT is based on a single study with a median follow up of only 2 years and 5 months (1) The study protocol included subsequent administration of External Beam Radiotherapy in the IORT arm based on pathology.

This study found a statistically significantly increase in local recurrence rates in the IORT arm, notwithstanding the short median follow up. While there was a low incidence of recurrences in both arms of the study, this is likely due to the short follow up period and the selection of favourable patients for entry into the study.

The Committee is concerned about the risk of an increase in local recurrences with IORT compared with external beam irradiation. The study and published critiques of the study are discussed further in the appendix below.

The Committee recommends that the use of lumpectomy and IORT be confined to clinical studies.

This approach aligns with the major guidelines in Oncology such as Up-to-date, ASTRO, NCCN, and NICE – see Appendix.

The SASCRO Committee will review new data and International Guidelines on IORT with an open mind. This will be reviewed in the first quarter of each year and when new data becomes available.

Yours Sincerely,

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Samuel Fourie
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SASCRO Executive Committee Members

APPENDIX:
Phase III study

There is only one phase 3 study of Kilovoltage IORT for breast cancer- the "TARGIT" study (1)

The study compared a "risk-adapted" approach to IORT comparing KV IORT to whole breast RT. If adverse features were found on the final pathology, then EBRT was added to the IORT (22% of patients in the IORT arm went on to receive EBRT). A protocol amendment was made in 2004 allowing randomisation AFTER surgery – necessitating re-opening of the wound and subsequent IORT as a second procedure

The table below describes the difference in the binomial proportions of local recurrences of the conserved breast and the associated p-values.

	Median follow-up	Number of events	Absolute difference (90% CI) in the binomial proportions of local recurrence* in the conserved breast (TARGIT minus EBRT)	Z score	$p_{non\text{-}inferiority}$
Whole trial					
All patients (n=3451)	2 years 5 months	34	0·72% (0·2 to 1·3)	−5·168	<0·0001
Mature cohort (n=2232)	3 years 7 months	32	1·13% (0·3 to 2·0)	−2·652	0·0040
Earliest cohort (n=1222)	5 years	23	1·14% (−0·1 to 2·4)	−1·750	0·0400
Prepathology†					
All patients (n=2298)	2 years 4 months	16	0·37% (−0·2 to 1·0)	−5·954	<0·0001
Mature cohort (n=1450)	3 years 8 months	14	0·6% (−0·3 to 1·5)	−3·552	0·0002
Earliest cohort (n=817)	5 years	9	0·76% (−0·4 to 2·0)	−2·360	0·0091
Postpathology‡					
All patients (n=1153)	2 years 4 months	18	1·39% (0·2 to 2·6)	−1·503	0·0664
Mature cohort (n=782)	3 years 7 months	18	2·04% (0·3 to 3·8)	−0·429	0·3339
Earliest cohort (n=405)	5 years	14	1·8% (−1·2 to 4·8)	−0·382	0·3511

The prespecified non-inferiority margin was 2·5%. Mature cohort consisted of 2232 patients for whom data was previously reported in 2010. Earliest cohort excluded patients enrolled in the last 4 years of the study. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *Binomial proportion=number of recurrences/number of patients. †TARGIT given at same time as lumpectomy. ‡TARGIT given after lumpectomy, as separate procedure.

Table 3: Calculation of $p_{non\text{-}inferiority}$ for the whole cohort, the mature cohort, and the earliest cohort

This statistical difference between the 2 arms indicates a biological difference between the 2 forms of treatment. This holds even though the percentages; recurrences are described as within the pre-trial parameters for equivalence

There was no difference in overall survival between the 2 arms.

There have been significant criticisms of this study along the following lines

1. Incorrect use of the non-inferiority hypothesis (2)
2. Focussing attention on the most favourable subgroup rather than the prespecified patient population (2)
3. The period of follow up is not long enough to infer 5-year survival results (3)
4. A claim of increased cardiac related deaths in the EBRT arm is not supported by our current knowledge of the risks of cardiac disease and radiotherapy. The author considers that r did not have balanced risk factors in the two cohorts (4)

We believe that these findings are following a similar pattern to the prospective randomised trial of intra-operative electron beam and external beam irradiation in 1305 patients (5) . After a medium follow-up of 5.8

years, 35 patients in the intraoperative radiotherapy group and 4 patients in the external radiotherapy group had had an ipsilateral breast tumour recurrence (p<0・0001).

References:

1. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial.
   JS Vaidya et al. Lancet 2014; 383: 603–13
2. Radiotherapy for breast cancer, the TARGIT-A trial
   Jack Cuzick Lancet 2014; 383: 1716
3. Radiotherapy for breast cancer, the TARGIT-A trial
   JS Haviland et al. Lancet 2014; 383: 1716
4. Radiotherapy for breast cancer, the TARGIT-A trial
   J Yarnold et al Lancet 2014; 383: 1717-1718
5. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial
   Veronesi et al. Lancet Oncology 2013; 1269 – 1277

EXTRACTS FROM INTERNATIONAL GUIDLEINES:

1. UPTODATE:

Caution with intraoperative radiation therapy — Ongoing research is aimed at exploring other modalities of RT that will minimize toxicities without reducing effectiveness. An example of this is intraoperative radiation therapy (IORT), which condenses the entire therapeutic dose into a single fraction, permitting surgery and radiation to be completed in one day. At this time, however, we suggest that use of IORT be limited to a clinical trial because the available data suggest an association with a higher risk of in-breast tumor recurrences (IBTR). For patients in whom the duration of therapy required for standard WBRT is a concern, hypofractionated WBRT schedules are a viable option. (See 'Dosing and schedule' above.)

Two trials, the TARGeted Intraoperative radiation Therapy-A (TARGIT-A) and the External versus intraoperative RT (ELIOT) trials, suggest that IORT is associated with an increased risk of IBTR compared with WBRT (absolute increase of approximately 4 percent over five years) [46,47]. In women with high-risk breast cancers (eg, grade 3, ER-negative, or triple-negative), the absolute increased risk was on the order of 15 to 20 percent. Longer-term follow-up (at 10 to 15 years) is warranted.

2. ASTRO:

C. Low-energy x-ray IORT for PBI should be used within the context of a prospective registry or clinical trial, per ASTRO Coverage with Evidence Development (CED) statement. When used, it should be restricted to women with invasive cancer considered "suitable" for partial breast irradiation (Table 1) based on the data at the time of this review (MQE, recommendation rated as "Weak").

3. NCCN
   No mention IORT in its Accelerated partial breast irradiation (APBI) guidelines

4. The NICE guidelines
   Suggest caution and the use of a multidisciplinary approach – Jan 2018
   (https://www.nice.org.uk/guidance/ta501/chapter/4-Committee-discussion#conclusions)