Recent activities of the GEC-ESTRO Breast Cancer Working Group

The breast cancer working group of the Groupe Européen de Curiethérapie-European SocieTy for Radiotherapy and Oncology (GEC-ESTRO) has existed for more than 17 years and we are delighted that innovative and challenging achievements have been made in breast brachytherapy during the past few years.

We report here the most important points to all ESTRO members:

- The results of the phase III prospective randomised trial that compared whole versus partial breast irradiation were initially published in *The Lancet* (oncological outcome: Strnad V, et al. Lancet. 2016;387(10015):229-38) and then twice in *Lancet Oncology* (late toxicity: Polgár C, et al. Lancet Oncol. 2017;18(2):259-268; and quality of life: Schäfer R, et al. Lancet Oncol. 2018;19(6):834-84).
  All these results confirmed that, when multicatheter interstitial brachytherapy was used, adjuvant accelerated partial breast irradiation (APBI) after breast-conserving surgery in patients with early breast cancer was not inferior to adjuvant whole-breast irradiation (WBI) with respect to five-year local control, disease-free survival, or overall survival. Five-year toxicity profiles and cosmetic results were similar in patients who were treated with breast-conserving surgery followed by either APBI or conventional WBI, with significantly fewer grade 2–3 late skin side-effects after APBI compared with WBI. APBI was not associated with worse quality of life compared with WBI.
- In order to promote and spread the use of interstitial breast brachytherapy on a large scale, the working group published in the *Green Journal* the guideline from the ESTRO-Advisory Committee on Radiation Oncology Practice (ACROP) for interstitial multi-catheter breast brachytherapy as APBI alone or as boost (Strnad V, et al. Radiother Oncol. 2018;128(3):411-420). In this report, the working group highlighted the recent standards and guidelines for the use of APBI with different multi-catheter image-guided brachytherapy techniques. The group provided guidelines to ensure precise catheter insertion for coverage of the target volume and to guarantee high-quality dosimetry for both boost irradiations for breast cancer after WBI as well as for partial breast re-irradiation.
- The avoidance of salvage mastectomy for women who have experienced an ipsilateral breast tumour event represents another important research topic for the working group. During the 2018 (San Antonio) and 2019 (Chicago) American Society for Radiation Oncology (ASTRO) meetings, the group reported in oral communication the preliminary results of an analysis of matched cohorts by propensity score. This analysis compared salvage mastectomy against second conservative treatment for second ipsilateral breast tumour events (*ASTRO 2018*) and the mature oncological results and prognostic factors after second conservative treatments (*ASTRO 2019*). After a median follow-up of six years, APBI as classified by GEC-ESTRO was considered as a significant prognostic factor for third breast tumour events ($p = 0.01$) while a trend was observed for molecular classification and second ipsilateral breast tumour event location.
  In 2021, the group has published in the *Red Journal* the final report of the propensity-score matched cohort analysis, which analysed the data for 1327 patients who had ipsilateral breast tumour events and who underwent either salvage mastectomy or second conservative treatments based on lumpectomy plus multicatheter interstitial brachytherapy. A total of 754 patients were matched by propensity score (mastectomy: 377 pts; conservative treatment: 377 pts). After a median follow-up of 75.4 months, no differences were noted in five-year overall survival rates and cumulative incidences of third breast events between the mastectomy and conservative treatment groups (88% [95% CI, 83.0-90.8] vs. 87% [95% CI, 82.1-90.2], $p = 0.6$ and 2.3% [95% CI, 0.7-3.9] vs. 2.8% [95% CI, 0.8-4.7], $p = 0.4$, respectively). Similarly, no differences were observed for all secondary endpoints. Five-year cumulative incidence of mastectomy was 3.1% (95% CI, 1.0-5.1) (Hannoun-Levi JM et al., IJROBP 2021, in press).
- The working group is investigating protocols for very accelerated partial breast irradiation (VAPBI). The group recently published in *Brachytherapy* the feasibility and early results of a phase I/II multicentre prospective trial that was conducted by José-Luis Guinot (Guinot JL et al., Brachytherapy 2021, in press). VAPBI is feasible with the application of multicatheter interstitial brachytherapy that uses four fractions of 6.25 Gy or three fractions of 7.45 Gy over two or three days. No excess acute effects have been observed. With a mean follow-up of 20 months, late side-effects seem to occur at similar frequencies to those that occur in standard fractionation.

Currently, the working group is busy with three main projects:

- Vratislav Strnad and Csaba Polgár are the chairs of the project to analyse the 10-year updated results of the GEC-ESTRO APBI phase III trial. This new analysis will provide more mature and consistent results regarding long-term oncological outcomes and toxicity profiles.
- The group has proposed that a phase III multicentre prospective trial be conducted to compare the outcomes of treatment through VAPBI (16 Gy, one day) alone versus APBI (32 Gy, five days/30.3 Gy, four days) with five years of endocrine therapy (chairs JM Hannoun-Levi, V Strnad, C Polgar). This is due to the results of the GEC-ESTRO VAPBI phase I/II trial (3/4 fractions) and the results that have been published recently by the Nice team in the Single Fraction Elderly Breast Irradiation (SiFEBI)

phase II prospective trial, which evaluated a single dose of 16 Gy (Hannoun-Levi JM et al., Brachytherapy. 2020;19(1):90-96), along with recent publications that focus on the withdrawal of endocrine therapy in elderly patients who have low-risk breast cancer.

The main eligibility criteria of the planned phase III trial are: 1) patients must be aged over 60 years with 2) non-metastatic histologically proven early stage breast cancer (pT1-2 < 30 mm) and 3) clinical/pathological N0 (cN0 and pN0) stage, with 4) luminal A-like/B-like molecular status. The primary objective of this phase III trial is to test the non-inferiority between the two therapeutic strategies over time in terms of disease-free survival with a 4% difference between the two arms. A population of 840 patients (420 per arm) would be required. The rationale of this prospective trial has been submitted for publication and is currently under review with the title “endocrine therapy with accelerated partial breast irradiation or exclusive very accelerated partial breast irradiation for women aged ≥ 60 years with early stage breast cancer (EPOPE). The rationale for a randomised phase III controlled trial”.

- In order to refine the eligibility criteria for a second conservative treatment after a second ipsilateral breast tumour event, the working group plans to update its multicentre database. With an international cohort of more than 500 pts, it will be possible to highlight, both deeply and precisely, the oncological prognostic factors that help in the decision-making process.

The working group is deeply involved and dedicated to the promotion of multicatheter interstitial brachytherapy. With use of APBI and VAPBI and the aim to avoid breast mutilation in case of local relapse, the group is contributing to paradigm shifts in breast-cancer treatment.

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