The status of radiotherapy in the management of breast cancer 2013

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Introduction

Radiotherapy is still widely and routinely used in the treatment of breast cancer, mainly as adjuvant treatment post lumpectomy or post mastectomy. Bourgier *et al.* [1] reviewing 75 articles found that 50 Gy in two Gy fractions plus a "booster dose" of 16 Gy in two Gy fractions *"is still the standard of care".* For patients with special risk factors, they conceded that accelerated fractionation (AF) or accelerated partial breast irradiation (APBI) may be considered. To ensure optimal planning for whole breast radiotherapy of any kind (WBRT), the wound margins should be marked with clips by the surgeon. Kirby *et al.* [2] showed that five markers may be optimal: one deep, and four radial; computed tomography (CT) imaged, clip based delineation of the tumor bed was found adequate. A useful free downloadable program is called *Adjuvant! Online* that gives the oncologist and the patient information on what the likely benefits of adjuvant radio-chemotherapy may be for a given patient. For a busy oncologist and an inquisitive patient, this is a convenient tool.

Accelerated partial breast irradiation (APBI): the new gold standard for early breast cancer?

Azria and Bourgier [3] suggest that partial breast irradiation may be the new standard for selected patients conforming to the ASTRO and GEC-ESTRO guidelines; the guidelines are readily available on the Internet. Since APBI is of fairly recent use, data younger than five years were preferred.

Brief historical perspective: radiotherapy is an integral part in the evolution of breast conservation

The trend towards *greater conservatism* of breast cancer treatment using radiotherapy as adjunct to surgery began with Prof. Robert McWhirter [4], a Scottish and Forbes professor of Medical Radiology (Edinburgh University). He obtained diplomas in both surgery and radiology (under the famed radiotherapist Ralston Paterson) and pioneered the establishment of good radiology *and radiotherapy* departments. H e proved in the 1950's to the skeptically aggressive surgeons at the time, that *simple mastectomy followed by well applied radiotherapy* gave results equal to that of radical mastectomy.

Umberto Veronesi *et.al.* [5] pioneered *breast conservation* therapy, eliminating the need for mastectomy in many women with early stage breast cancer. They showed that quadrantectomy plus axillary dissection was equivalent to mastectomy plus axillary dissection, *provided that quadrantectomy was supplemented by a full course of radiotherapy.*

Bernard Fisher (USA) [6] pioneered the more conservative *"lumpectomy"* for noninvasive and invasive early stage breast cancers. Project 13-06 of the NSABP compared modified radical mastectomy vs lumpectomy alone to lumpectomy plus radiotherapy for Stage I-II breast cancers. They concluded in the 1990's that "all the evidence continues to justify the use of lumpectomy plus radiotherapy for the treatment of invasive breast cancer".

In 1998 {study B-17} Fisher *et al.* [7] showed that the above held true for *intra-ductal carcinoma,* Lumpectomy plus radiotherapy reduced the incidence of 'in breast tumor recurrence' (IBT) from 13.4% to 8.15% for non-invasive cancers ($p = 0.007$) and from 13.4% to 3.9% for invasive cancers ($p < 0.0001$) after eight years of follow-up.

Is a six week course of radiotherapy always necessary? Veronesi *et al.* [8] introduced *Intra-operative radiotherapy (IORT)* for breast cancer with an electron beam using a newly developed mobile linear accelerator that could be pushed into the theater. They used a *single dose* of 21 Gy to the tumor bed instead of using a five-week course of radiotherapy. The *principle of single dose APBI* was born and radiobiologically makes sense only for microscopic residual disease.

Historically then, radiotherapy has been the central player in the quest for ever greater breast conservative therapy and for palliation of brain and bone metastases.

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Table 1. — *The dose fall-off with Ir^{192} point sourced spherical applicators (based on the inverse square law) and the influence of the size of ball or balloon on the radiation dose distribution. The EQ2 (dose equivalent to the effect of a dose obtained with conventional two Gy fractions) is given in brackets for an α/β ratio = four Gy. The α/β ratio is a measure of sensitivity of tissues to fraction sizes.*

Diameter of ball	Surface dose Gy	Dose at 10 mm, α/β ratio = 4 Gy	Dose at 20 mm	Dose at 25 mm
2.0 cm; r = 1cm	84 Gy (1231 Gy)	21 Gy (87.49Gy)	9.3 Gy (20.7 Gy)	6.85 (12.4 Gy)
4.0 cm; r = 2cm	*47.25 (403.6 Gy)*	*21 Gy (87.49 Gy*	*11.8 Gy (30.0 Gy)*	*9.3 (20.7 Gy)*
6.0 cm; r = 3cm	37.23 (255.8 Gy)	21Gy (87.49Gy)	13.4 Gy (39.0 Gy)	10.7 Gy (26.3 Gy)

Is radiotherapy really effective?

Standard tangential fields: specific studies by Fletcher [9,10] determined that the radiation dose needed to eradicate subclinical deposits of cancer cells 90%- 95% of the time is about 45 Gy to 50 Gy; larger doses are needed for clinically obvious tumors. This is so for *standard tele-therapy with Cobalt units or linear accelerators.* For the new trend to administer intra-operative adjuvant radiotherapy to eradicate microscopic residual disease for early cancers, electrons (from linear accelerators),brachy-therapy units, either radioactive isotopes or 50 kV X-ray units, were developed.

Dose distribution issues with the new spherical applicators.

Table 1 shows the non-homogeneous dose distribution around spherical applicators with a central point source – the dose ranges from "overkill" at the surface of the applicators to "barely sufficient" at 20 mm away (Table 1). This is a matter of concern for radiation oncologists. However, new studies show that the radiation dose is probably adequate up to about 23 mm from the applicator surface for balloon type applicators with an Ir^{192} point source: Herskind *et al.* [11] proposes the concept of a *"sphere of equivalence"* around spherical applicators; i.e. a dose equivalent in to that of a dose of 60 Gy in two Gy fractions up to about 25 mm from the applicator surface. They argue *inter alia* that there is evidence that immediate post-op irradiation is more effective because it arrests cell growth that would otherwise result from the growth-stimulating 'soup' of factors released by the surgery. Delayed radiotherapy loses this advantage.

For a 40 mm diameter ball type applicator, the effective dose 20 mm from the surface is 30.0 Gy (EQ2) which is still enough to reduce the number of viable cells to about one surviving mammary cell out of 1,000 [12]. For micro-tumors of four^3 mm, the dose required to kill 50% of the tumors is 45.75 Gy [13].

It is interesting to note that for a 40-mm diameter sphere and the dose prescribed at ten mm the volume effectively irradiated is about 42 cm^3 or ten times the volume of a two-cm diameter tumor which is three time more than tissue (12 cm^3) removed by the surgeon for a two-cm diameter tumor (volume about four cm^3). More information about volumes and dose distributions with respect to a major clinical trial is discussed by Smit [14].

Radiation delivery systems used and the associated clinical results.

A. Conventional linear accelerators.

These have developed enormously over the last decade as will become clear. They offer a choice of photon energies (usually two) and several electron energies. Electrons have the very useful quality that the depth of penetration of the radiation energy is dependent on the energy. For instance a six MeV beam will penetrate approximately 20 mm (about 1/3 of the nominal energy in centimeters) while the tissues underneath are spared; photons are far more penetrating. The new accelerators have built in position checking ability, multi-leaf collimators etc.

Linear accelerator based radiotherapy is used in several forms: *whole breast radiotherapy (WBRT)* which can be ***c****onventionally* fractionated over 33 days *or hypo-fractionated* over 16 days. Obviously this is also accelerated fractionation (AF).

Results of WBRT: 50 Gy in 25 fractions +/- a booster dose of ten to16 Gy in two Gy fractions Is the universally accepted standard therapy as stated above. This approach gives good results with the local recurrence rate at ten years about six percent, Bartelink *et al.* [15]. For early breast cancers, this figure may be as low as 2.5%.

Hypo-fractionated WBRT: a large study of this abbreviated type of conventional radiotherapy comes from Ontario, Canada - (The Ontario Clinical Oncology Trial), Ashworth *et al.* [16]. who retrospectively analyzed data for > 41,000 post-lumpectomy patients who received either 16 or 25 fractions; the results were equivalent and resulted in about 70% of the patients surveyed being so treated. In an excellent review, Yarnold *et al.* [17] concluded that the results of recent randomized trials justify the routine use of "modest hypo fractionation" for adjuvant whole breast irradiation. Regimens used include the United Kingdom schedule of 40 Gy in 15 fractions (EQ2 dose,α/β ratio of 4.0) is 44.4 Gy. The authors prefer 42.5 Gy in 16

fractions (EQ2 = 47.14 Gy). Whelan *et al.* [18] compared 13-16 fractions (3.2 Gy or 2.65 Gy) given to 622 patients treated by hypo-fractionation to 612 patients treated by the standard EBRT regimen, the results were the 'the same'.

From the current information, one could conclude that a hypo-fractionated regimen is acceptable for the routine treatment of patients that would normally receive 50 Gy in two Gy fractions. Most centers use a central "boost of ten to 16 Gy in two Gy fractions; Hypo-fractionated boosts would add another three days to the regimen if used.

Accelerated partial breast irradiation (APBI) by means of a linear accelerator:

Multileaf collimators and intensity modulation of photons made *conformal therapy of post-lumpectomy sites- not cavities*- practical. Conformal therapy has the advantage that the wound can be closed and no further interventions/operations are needed.

Bondiau *et al.* [19] showed during a dose escalation study (highest 25 Gy in three fractions; EQ2 = 51.3 Gy) that for patients who do not qualify for breast conserving therapy, neo-adjuvant chemotherapy followed by *highly conformal stereotactic radiotherapy* followed by surgery could yield pathology based complete responses (pCR) of 36% with the ability to achieve a 92% breast conservation rate in this cohort. This did not result in any complications relating to the surgery (lumpectomy eight weeks after the last chemotherapy dose). One case of serious skin toxicity occurred due to the radiotherapy. The authors find that a phase II trial will be justified. This is an interesting approach and could in principle extend the number of patients that could avoid mastectomy. This approach should preferably be within the context of a clinical trial.

Special, dedicated mobile electron accelerators were developed.

Examples are the *"Mobetron"* and the *Novac -7*. These systems are expensive. Veronesi *et al*. [8] first used intra-operative electron therapy (IORT), where the electron applicator is placed in virtual contact with the flat, opened up, wound surface. *The dose of 21 Gy is given in one single session (EQ2 = 80 Gy; α/β=4) A single dose of 18 Gy would be equivalent to 66 Gy).Results* after quadrantectomy were reported by Veronesi *et al.* [20] on 1,822 patients so treated (January 2000 to December 2008). The tumors were invasive carcinomas < 2.5 cm in diameter treated by quadrantectomy followed by intra-operative electron therapy (ELIOT). The results were as follows: the mean follow-up period was 36.1 months, 42 women (2.3%) developed local recurrence, 24 (1.3%) developed a new primary in the ipsilateral breast, 26 (1.4%) developed distant metastases; 46 (2.5%) died of carcinoma, the other of other causes. The five-year survival rate was 97.4% and the ten- year survival rate was 89.7%. Complications: fat necrosis, was observed in 4.2% of the patients but usually caused no problems, and 1.8% had significant fibrosis. *They concluded that the results appeared promising.*

Leonardi *et al.* [21] reported the results of an electron (ELIOT) APBI trial in 2013. The guidelines of the European Society for Therapeutic Radiology and Oncology ("GEC-ESTRO)" were used to stratify the patients with early breast cancer. The same 1,822 patients were analyzed, and of these, 573 candidates fell into the "good candidates group. The five-year in breast recurrences for this group was 1.9% and in the two less favorable groups, 7.4% and 7.7%, respectively. The GEC ASTRO guidelines separated the low risk group from the two higher risk groups, but not the latter from each other. (Compare the above results to the in- breast recurrence rate for conventional whole breast irradiation of about six percent for early stage tumors).

Leonardi *et al.* [22], using the same 1,822 patients following the American Society for Therapeutic Radiation Oncology (ASTRO) guidelines which identifies three risk groups, although slightly different to the European guidelines. They concluded that the ASTRO guidelines differentiated better than the GEC ESTRO guidelines between the risk groups.

Fibrosis: Rampinelli *et al.* [23] compared APBI (ELIOT) and whole external breast radiotherapy (EBRT) with reference to the incidence and severity of fibrotic changes induced in the lungs; 178 patients were, prospectively studied. The dose used was 21 Gy as a single dose prescribed at the 90% isodose vs a 50 Gy dose EBRT plus a ten Gy boost in two Gy fractions. Pulmonary fibrosis was assessed in 83 in the EBRT arm and 96 in the ELIOT arm. All patients had infiltrating carcinoma with lesions < 2.5 cm in diameter. Of 42 patients who had developed pulmonary fibrosis, 38 or 90% were in the EBRT arm and four (about 10%) in the ELIOT arm ($p < 0.0001$). Of these, 26 were grade 1 (one in ELIOT), 15 were grade 2 (three in ELIOT), and only one was grade 3.

Safety of the mobile linear accelerators: Giocca *et al.* [24] found that the mobile linear accelerators were safe for use in the operating room, i.e did not need dedicated shielded rooms- a major advantage (also shared by the 50kV X ray units-see later). The safety level depended to some extent on patient load. No extra shielding was required.

Robotic linear accelerators like the "cyberknife" for body stereotactic radiotherapy

(Body SRT): a very high dose of radiation can be delivered to *a very small volume of tissue for example lesions in the brain lung or liver.* Very high doses confined to very small volumes of tissue (< ten cm^3] causes relatively little damage to surrounding structures. There are not many of these in use; modern linear accelerators can do much the same.

Proton therapy: These units are physically huge very costly and cumbersome; apart from that they can do what modern linear accelerators can do, in some cases with more sparing of normal tissues.

B. Lumpectomy cavity irradiators:

An excellent review of the available APBI techniques is offered by Njeh *et al.* [25]. It gives excellent pictorial details of the hardware available and also the clinical results up to 2010. A book on the subject of APBI was recently published [26].

C. Spherical applicators with radionuclide point sources.

Inflatable balloon systems using a central catheter with a central Ir ^{192} point source include the *Mammosite* balloon which is inserted into the lumpectomy cavity, the wound is closed around the catheter and the total dose is delivered in ten fractions over five days.. Thereafter the balloon is deflated and removed with relatively little discomfort.

Clinical results: This scheme demands that at least six hours must elapse to allow repair of sub-lethal radiation damage.This is a nuisance for department and patient alike.

Some institutions compared three different methods, like the William Beaumont Hospital group. A recent report on 2,127 patients so treated used three types of APBI: interstitial, balloon type and 3D conformal radio-therapy. The median age of the patients was 65 (32-94) years, median tumor size ten mm (0-45mm) and median follow-up 60.6 months. Intra-breast tumor recurrence (IBTR) was observed in 2.8%, regional node failure in 0.6% and metastatic disease in 1.6% of the entire cohort. The IBTR was not significantly different between the ASTRO and CS ESTRO guideline groups (suitable' 'cautionary' or 'unsuitable') These results are impressive even if the guidelines failed to separate the population into categories [27]. A similar trial is ongoing- The NSABP 39/RTOG 0413 that will compare 'standard radiotherapy" 60 Gy in 30 fractions, Iridium type balloon *MammoSite"* and 3-D conformal radiotherapy. The trial aims to include 4,700 patients.

Inflatable balloon devices using multiple catheter arrangements for improved dosimetry.

Examples are the *Strut Adjusted Volume Implant* '*SAVI"* and *ClearPath* and the *Mammosite Multi.* Some data are available in this respect. A study by Sato *et al.* [28] reported on 184 patients so treated in Japan. A total of 120 patients with pN0 tumors and mean age 55 years who had at least one year's follow-up were reported on. APBI was initiated on the same day as the surgery, and eight fractions of four Gy each were given over five to six days with a 2- mm margin coverage. The ten-year risk of in breast tumor recurrence (IBTR) was calculated using a web-based tool *IBTR!* The median follow-up period was 3.1 years (1.1 -4.4 years range); 96% of tumors were less than two cm in diameter and 89.4% were ER+. Hormone treatment was used in 86% of the patients and adjuvant chemotherapy in 20% of the patients. They estimated that if all the patients in this group would have received WBRT, the IBTR would be 1.1 to 2.8; for the study patients only one IBTR was observed (< 1%) and none occurred in the tumor bed. The authors concluded that multi-catheter APBI would give results equal to WBRT.

Spherical applicators with miniature X ray with 50 kV "point" sources of radiation.

The radiation source for these devices is a miniature X ray machine (easily shielded) and not a radionuclide like Ir*192*. The 50 kV sources are mobile and easily shielded, and can be pushed into the theater; they should be considerably cheaper than mobile linear accelerators.

Multicatheter types: An example is *Axxent*. The dose can be fractionated over days via multiple catheters that enables more satisfactory dose distributions yet retaining the benefit of the balloon type of device.

Rigid hollow ball types like "Intrabeam" uses hollow ball type applicators. The total dose must be delivered in a *single session.* Results: Grobmeyer *et al.* [29] reported their results in 78 patients so treated. The relative biological effectiveness (RBE) of 50 kV X rays is = one at the surface and two at 20 mm so that the nominal dose must be multiplied by this factor. An applicator of suitable size is inserted into the lumpectomy cavity and the tumor bed is then irradiated. The total operative time including the lumpectomy, sentinel lymph node dissection, and the *Intrabeam* (IB) treatment ranged from 79 minutes to 232 minutes with a mean time of 132 minutes. At 12 months follow-up, the cosmetic results were reported to be good to excellent in 92% of the patients and no local recurrences were seen in the follow up period (November 2010 to October 2012). The costs calculated for the *Intrabeam* device came to USD 1,857.00, which is far less than a course of conventional tele-therapy at USD 9,658.00. They concluded that the safety, ease of use, and reduced costs argues for more widespread use of the method. Experience is limited at this stage; more data must be obtained.

There was lively correspondence after the publication by Vaidya *et al.* [30] of their results of the "'TARGIT" (*Intrabeam*) trial. Reitsamer *et al.* [31] at the time felt that the follow-up is much too short to be overconfident. Smith *et al.* [32] felt that the doses were inadequate and just delayed recurrences. Haviland *et al.* [33] warn that recurrence may occur many years later and that conclusions are immature. Cameron *et al.* [34] disagrees that the TARGIT trial data give "robust and mature" evidence. They concur with the ASTRO consensus statement that on PBI "That women should be informed about the much longer track record of safety and efficacy of post-operative whole breast irradiation". They like wise would like

to see mature outcome data from TARGIT A before it can be regarded as safe. The rebuttal by Vaydia *et al.* [30] however, has good arguments to support their conclusions, especially that older women 60 years and older will be spared the rigors of a protracted course of radiotherapy, yet will probably enjoy the full benefit of WBRT by availing themselves of the intra-operative APBI technique.

Interstitial volume implants. These are still being done, but it implies a second surgical procedure after a lumpectomy or a quadrantectomy. Guide tubes are placed and later filled with Ir^{192} wires, or by LDR (low dose rate) or HDR after-loading systems. The patients need to be isolated for either the manual or LDR afterloading.

Complications

Many articles addressed the problem of cardio-toxicity due to radiotherapy. Nowadays the anterior descending coronary artery (ADCA) should routinely be identified and specifically excluded from radiation. Mediastinal irradiation may induce cardiomyopathy, damage to valves, pericarditis, etc. Multidiciplinary teams are advised when the mediastinum needs to be irradiated.

Developments that may impact on the future use of radiotherapy

ER, PR and Her 2 receptors are integrated with tumor grade to define new classes of breast cancer with different prognoses. These groups or classes may require different therapeutic approaches. The *luminal* cells are the cells lining the breast ducts. Examples are:

- Luminal A, (ER+ and low grade,36% of tumors - for hormonal Rx alone?);
- Luminal B, (Er+ and high grade, Subtype 1: HER2 - 26% of tumors),Subtype 2: ER+ and high grade, HER 2 +; 19% of tumors);
- ERBB2/HER2+ (non-luminal) with *amplified* HER2/neu (19% of tumors);
- Normal breast-like tumors;
- Basal like ER-, PR-, HER2- or *triple negative breast tumors (TNBT).-most BCR1 tumors are triple negative* (12.9% of tumors);
- Luminal ER-/AR+; *androgen responsive subtype* that may respond to the anti-androgen bicalutamide (androgen receptor: AR) after failure to respond to tamoxifen/aromatase inhibitors and
- Claudin – low, frequently triple negative, lacking E-cadherin expression, often with lymphocyte infiltrate.

Yanagawa *et al.* [35] evaluated 363 tumors and found the percentage distribution as given; above and it seems clear that many more factors may have to be taken into account when selecting patients for treatment; some may not need radiotherapy, others may well need a redefined hormonal treatment or a combination of hormonal (including androgens), chemotherapeutic, and radio-therapeutic approaches. These findings may signify the need for a whole host of new clinical trials.

Proteomics: Somiari *et al.* [36] pointed out that proteomics may offer bedside diagnostic tests to determine the presence of malignant breast tissue- a possible paradigm shift in early diagnoses and it obviously may have a major impact on diagnosing recurrent tumor. All these developments will eventually impact further how radiotherapy is going to be used in the future; for the moment it remains a powerful therapeutic modality for breast cancer. Imaging techniques to detect viable tumor cells may come in very handy, like positron emission tomography/CT scans and functional magnetic resonance imaging.

References

[1] Bourgier C., Aimard L., Bodez V., Bollet M.A., Cutuli B., Franck D., *et.al.*: "Adjuvant radiotherapy in node negative patients with breast cancer: a qualitative and systematic review". *Crit. Rev. Oncol. Hematol.,* 2013, *86*, 33.

[2] Kirby A.N., Jena R., Harris E.J., Evans P.M., Crowley C., Gregory D.L., Coles C.E.: "Tumor bed delineation for partial breast/boost irradiation: what is the optimal number of implanted markers?" *Radiother. Oncol.,* 2013, *106*, 231. doi: 10.1016/j.radonc.2013.02.003. Epub 2013 Mar 13.

[3] Azria D., Bourgier C.: "Partial breast Iraadiation: new standard for selected patients". *Lancet,* 2010, *376*, 71. doi: 10.1016/S0140-6736(10)60898-7. Epub 2010 Jun 10

[4] McWhirter R.: "Simple mastectomy and radiotherapy in the treatment of breast cancer". *Br. J. Radiol.,* 1955, *28*, 128.

[5] Veronesi U., Saccozzi R., Del Veccho M., Banfi A., Clemente C., De Lena M., *et al.*: Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers". *N. Engl. J. Med.,* 1981, *305*, 6.

[6] Fisher B., Anderson S.: "Conservative surgery for the management if invasive and non-invasive carcinoma of the breast: NSABP trials". *Am. J. Surg., 1994, 18*, 63.

[7] Fisher B., Diguan J., Wolmark N., Mamounas E., Costantino J., Poller W., *et al.*: "Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17". *J. Clin. Oncol*., 1998, *16*, 2.

[8] Veronesi U., Gatti G., Luini A., Intra M., Ciocca M., Sanchez D., *et al.*: "Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery. *Arch. Surg.,* 2003, *138*, 1253.

[9] Fletcher G.H.: "Clinical dose-response curve of subclinical aggregates of epithelial cells and its practical application in the management of human cancer". In: Friedman, M. (ed). *Biological and clinical cases of radiosensitivity.* Springfield, Charles C. Thomas, 1974, 485.
[10] Fletcher G.H.: "History of of irradiation in the primary management of apparently regionally confined breast cancer". *Int. J. Radiat. Oncol. Biol. Phys.,* 1985, 11, 2133.
[11] Herskind C., Griebel J., Kraus-Tiefenbacher U., Wenz F.: "Sphere of equivalence--a novel target volume concept for intraoperative radiotherapy using low-energy X rays". *Int. J. Radiat. Oncol. Biol. Phys.,* 2008, *72*, 1575. doi: 10.1016/j.ijrobp.2008.08.009.
[12] Hall E.J.: "Radiobiology for the radiologist". 3rd ed. Philadelphia, Lippincott, 1988, 56.
[13] Hall E.J.: "Radiobiology for the radiologist". 3rd ed. Philadelphia, Lippincott, 1988, 73.
[14] Smit B.J.: "Could the eventual results of the NSABP* 39/RTOG** 0413 trial for partial breast irradiation (PBI) be improved by combining spherical applicators and whole breast irradiation? Radiobiology suggests it may". *Eur. J. Gynaecol. Oncol.,* 2010, *3*, 241.
[15] Bartelink H., Horiot J.C., Poortmans P.M., Struikmans H., Van den Bogaert W., Fourquet A., *et al.*: "Impact of a higher radiation dose on local control and survival in breast conserving therapy of early breast cancer: 10 year results of the randomized boost versus no boost EORTC 22881-10882 trial". *J. Clin. Oncol.,* 2007, *25*, 3259. Epub 2007 Jun 18.
[16] Ashworth A., Kong W., Whelan T., McKillop W.J.: "A population based study of the fractionation of post-lumpectomy breast radiation therapy". *Int. J. Radiat. Oncol. Biol. Phys.,* 2013, *86*, 51.
[17] Yarnold J., Bentzen S.M., Coles C.: "Hypo-fractionated whole breast radiotherapy for women with early breast cancer; myths and realities". *Int. J. Radiat. Oncol. Biol. Phys.,* 2011, *79*, 1.
[18] Whelan T.J, Pignol J.P., Levine M., Julian J.A., MacKenzie R., Parpia S., *et al.*: "Long term results of hypo-fractionated radiotherapy for breast cancer". *N. Engl. J. Med.,* 2010, *362*, 512. doi: 10.1056/NEJMoa0906260.
[19] Bondiau P.Y., Courdi A., Bahadoran P., Chamorey E., Queille-Roussel C., Lallement M., *et al.*: "Phase 1 clinical trial of stereotactic body radiation therapy concomitant with neoadjuvant chemotherapy for breast cancer". *Int. J. Radiat. Onc Biol. Phys.*, 2013, 85, 1193. doi: 10.1016/j.ijrobp.2012.10.034. Epub 2013 Jan 16.
[20] Veronesi U., Orecchia R., Luini A., Galimberti V., Zurrida S., Intra M., *et al.*: "Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons.". *Breast Cancer Res Treat.,* 2010, *124*, 141. doi: 10.1007/s10549-010-1115-5. Epub 2010 Aug 15.
[21] Leonardi M.C., Maisonneuve S.P., Mastropasqua M.G., Morra A., Lazzari R., Dell'Acqua V., *et.al:* "Accelerated partial breast irradiation with intra-operative electrons: using GEC-ESTRO guidelines for patient selection". *Radiother. Oncol.*, 2013, *106*, 21. doi: 10.1016/j.radonc.2012.10.018. Epub 2012 Dec 3.
[22] Leonardi M.C, Maisonneuve S.P, Mastropasqua M.G., Morra A., Lazzari R., Rotmensz N., *et.al.*: "How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology.". *Int. J. Radiat. Oncol. Biol. Phys.,* 2012, *83*, 806. doi: 10.1016/j.ijrobp.2011.08.014. Epub 2012 Jan 13.
[23] Rampinelli C., Bellini M., Ivaldi C.D., Intra M., Raimondi S., Meroni S., *et.al.*: "Assessment of pulmonary fibrosis after radiotherapy (RT) in breast conserving surgery: comparison between conventional external beam RT (EBRT) and intraoperative RT with electrons (ELIOT)". *Technol. Cancer Res. Treat*., 2011, *4*, 323.
[24] Giocca M., Pedroli G., Orecchia R., Guido A., Cattani F., Cambria R., Veronesi U.: "Radiation survey around a Liac mobile electron linear accelerator for intraoperative radiation therapy.". *J. Appl. Clin. Med. Phys.,* 2009, *10*, 2950.
[25] Njeh F., Saunders M.W., Langton C.: "Accelerated partial breast irradiation (APBI): a review of available techniques". *Radiat. Oncol.,* 2010, *5*, 90.
[26] Wazer D.E., Arthur D.N., Vicini F.A. (eds). "Accelerated partial breast irradiation. Techniques and clinical implementation". Heidelberg: Springer-Verlag, 2009.
[27] Wilkenson J.B., Beitsch P.D., Shah C., Arthur D., Haffty B.G., Wazer D.E., *et al*.: "Evaluation of current consensus statement recommendations for accelerated partial breast irradiation (APBI): a pooled analysis of the William Beaumont Hospital and American Society of Breast Surgeon MammoSite Registry Trial Data". *Int. J. Radiat. Oncol. Biol. Phys.,* 2013, *85*, 1179. doi: 10.1016/j.ijrobp.2012.10.010. Epub 2012 Nov 22.
[28] Sato K., Mizunu Y., Fuchikami H., Kato M., Shimo T., Kubota J., *et al.*: "Individualized case control study of accelerated partial breast irradiation by multi-catheter brachytherapy in Japanese patients with breast cancer". *Cancer and Clinical Oncology, 2013, 2*, 127.
[29] Grobmeyer S.R., Lightsey J.L., Bryant C.M., Shaw C., Yeung A., Bhandare N., *et al.:* "Low-kilovoltage single dose intra-operative therapy for breast cancer: results and impact on a multidisciplinary breast clinic program". *J. Am. Coll. Surg.,* 2013, *216*, 617. doi: 10.1016/j.jamcollsurg.2012.12.038. Epub 2013 Feb 14.
[30] Vaidya J.S. Joseph D.J. Tobias J.S., Bulsara M., Wenz F., Saunders C., *et al.*: "Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial". *Lancet,* 2010, *376*, 91. doi: 10.1016/S0140-6736(10)60837-9.
[31] Reitsamer R., Fastner G., Kapp M., Menzel C., Sedlmayer F.: "Intraoperative radiotherapy for early breast cancer". *Lancet,* 2010, *376*, 1141. doi: 10.1016/S0140-6736(10)61529-2.
[32] Smith, B.D., Bucholz T.A., Huehrer H.: "Intraoperative radiotherapy for breast cancer". *Lancet, 2010,* 376, 1141. doi: 10.1016/S0140-6736(10)61530-9.
[33] Haviland J S, Hern RA, Bliss J: "Intraoperative therapy for breast cancer". *Lancet*, 2010, *376*, 1142. doi: 10.1016/S0140-6736(10)61531-0.
[34] Cameron D., Kunkler I., Dixon M., Jack W., Thomas J., Kerr G.: "Intraopterative radiotherapy for breast cancer". *Lancet,* 2010, *376*, 1142. doi: 10.1016/S0140-6736(10)61532-2.
[35] Yanagawa M., Ikemot K., Kawauchi S., Furuya T., Yamamoto S., Oka M., *et. al.*: "Luminal A and Luminal B (HER2 negative)subtypes of breast cancer consist of a mixture of tumours with different genotype". *BMC Res. Notes,* 2012, *5*, 367. doi: 10.1186/1756-0500-5-376.
[36] Somiari R.I., Sullivan A., Russel S., Somiari S., Hu H., Jordan R., *et al.*: "High through-put proteomic analysis of human infiltrating duct carcinoma of the breast". *Proteomics,* 2003, 10, 1863.

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