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Special Issue on Radiation Therapy for Breast Cancer - Radiation Side Effects -

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ABSTRACT

Post-operative radiotherapy after conservative surgery or mastectomy improves disease free and overall survival. Collateral effects and toxicity dramatically decreased in the last decades due to technological innovations (i.e. conformal techniques, respiratory gating, image-guided radiotherapy, tracking systems), less demolitive surgical approaches, new reconstructive techniques and better knowledge of radiotherapy interaction with chemo/hormono/immunotherapies.

A more careful consideration of patients co-morbidities and the collaboration of specialized personnel improves its safety too.

Even when loco-regional lymphnodes have to be irradiated, according to tumor stage and age of the patient, limited acute and late toxicity has been detected. The irradiation of regional lymphnodes draws our attention to thyroid and brachial plexus toxicities in addition to the cutaneous, cardiac and pulmonary ones.

Keywords: Radiotherapy; Breast Cancer; Cutaneous Toxicity; Cardiac Toxicity; Pulmonary Toxicity; Thyroid Toxicity; Brachial Plexus Toxicity

INTRODUCTION

Breast cancer is the most common female malignancy in the western countries and is the second leading cause of malignant deaths. A large proportion of breast cancer patients receive post-operative radiation therapy after conservative surgery and mastectomy to decrease locoregional recurrence rates and improve overall survival [1,2].The irradiated volumes i.e. whole breast, tumoral bed, chest wall, regional lymph nodes (internal mammary chain, supra/infraclavicular and axillary nodes) could vary, according to international guidelines, taking into account patient and tumor characteristics.

The duration of radiotherapy strictly depends on the irradiated volume, dose/fraction and total dose and lasts between 1 day, in case of intraoperative RT, and nearly 7 weeks, in case of conventional whole breast RT plus booster dose on surgical bed.

Side effects and toxicities widely vary as a consequence of patients features and attitudes, irradiated volume, total dose, dose/fraction, radiotherapy technique and systemic treatments.

Several grading scales exist to aid in the reproducible quantification of acute radiation toxicities. The Radiation Therapy Oncology Group/ European Organization for Research and

Treatment of Cancer (RTOG/EORTC) toxicity criteria and National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) systems are the most commonly used [3,4]. This review focuses on the main radiation side effects in adjuvant breast cancer treatment and discusses the strategies for the prevention and management of radiation-related toxicity.

SKIN TOXICITY

The effects of radiation on skin have been recognized as soon as radiation was introduced as a treatment modality [5-7]. Consequently researches have begun examining techniques to reduce radiation induced skin reactions, aided by the radio-biology evidences on fractionation modalities for improving normal tissue repair [6]. The introduction of the megavoltage units improved the skin sparing if compared with orthovoltage ones and consequently reduced toxicity [8].

Despite the effort, Radiation Dermatitis (RD) still continue to be the most common side effect of radiotherapy and could condition worse cosmesis and subsequently QoL[5].

Radiation affects the two main components of skin, epidermis and dermis, each of which respond variably to radiation exposure. High energy X-Rays leads to DNA breaks within the epidermis and dermis causing the so called syndrome of radiation dermatitis [6]. Radiation induced DNA damage within the epidermis disrupts normal proliferation and differentiation of basal keratinocytes, leading to the physical barrier lost [9-11].

By the other hand, the effects on dermis consists mainly of microvascular injury, activating proinflammatory cytokines, tTNF alfa and transforming growth factor: they contribute in both acute and late side effects of radiation, starting with inflammatory edema, erythema, desquamation, ulceration, telangiectasia , late tissue fibrosis [12-19].

Mechanism of RD developes in a dose dependent manner with predictable timing [12,20,21]. Acute skin reactions (defined as occurring within 30-90 days from radiation exposure) has a dose threshold development, starting with erythema at 6-10 Gy up and worse toxicity at 40 Gy or higher dose. Nearly around day 10 of treatment the re-epithelisation begins and competes with ongoing radiation damage to maintain the homeostasis of the epidermal layer. The majority of symptoms usually relieves in 2-4 weeks after the end of treatment, hyperpigmentation lasts some more months. Late side effects can appear months or years after the end of therapy [20-24].

RISK FACTORS

Many risk factors have been identified and categorized in treatment and patient related ones.

Treatment related factors

The negative impact of adjuvant systemic chemotherapy on acute and late toxicity has been spoted out and underlined in studies enrolling patients mainly receiving taxanes and/or anthracyclines based regimen [25-27], so that the concomitant use of radiotherapy and anthracyclines/taxanes based chemotherapy was not recommended.

Surgical approach is crucial for the cosmetic outcome too. The amount of resected tissue is considered one of the most relevant features concerning breast cosmesis. The kind of surgery, more or less radical, the new oncoplastic techniques and the different reconstructive surgery (i.e.expander, prosthesis or flap) are strictly related to radiotherapy toxicity. Nevertheless no clear data still exist on the best sequence of reconstruction and radiotherapy, the safer break between these procedures and the more appropriate radiotherapy techniques in this group of patients [28,29].

The evolution in radiotherapy delivery techniques, from

2dimension (2D) to 3D treatment planning, resultes in significantly less acute and long term toxicity. The 3D technique, taking into account changes in breast contour, reduces radiation induced skin reaction. Data from retrospective studies suggest that large dose inhomogeneity, occurring with the 2D techniques, predisposes to more severe acute skin reactions [30-33].

Advanced 3D techniques, Volumetric Arc Therapy (VMAT) and Intensity Modulated RadioTherapy (IMRT) are the main methods that allow multiple radiation fields for decreasing breast dose inhomogeneity. Prospective trials of 3D and IMRT techniques have shown decreased rates of acute and late radiation skin toxicity [34-36].

Radiotherapy delivered to patient in prone position could improve the dose distribution, reduce radiation hotspots and lower the incidence of breast dermatitis including moist desquamation [37].

Alternative treatment schedules, such as hypofractionated breast irradiation, is increasingly used [38] and safe in terms of local control and acute/late toxicity profile without negative impact on cosmesis. Three randomized trials (START A, START B and Canadian), which compared standard vs Hypofractionation (HF) in post-operative radiotherapy, suggest that HF reduces the rate of dermatitis, pruritus and hyperpigmentation [39,41]. In a recently published study [42] the authors conclude that HF is associated with a significantly reduction of severe acute skin reaction compared to the standard fractionation one: Grade 2 skin reactions were observed in 19% of the patients treated with CF compared to 2 % treated with HF.

Even and moreover with such a fractionation, large dose inhomogeneity (V >107%) has to be carefully detected and corrected for avoiding severe acute skin reactions.

The role of boost on cosmesis is still controversial, but a correlation with higher late toxicity is widely demonstrated by the results of the EORTC trial 22881-10882 [43,44].

Accelerated partial breast Irradiation (APBI) has been introduced as an alternative treatment method for selected patients with early stage breast cancer. Results concerning cosmetic outcome differ widely, ranging from good/excellent cosmetic results in 90% of the patients to 21% unacceptable cosmesis [45]. This variability strongly depends on the RT technique and moreover randomized trials are still ongoing for confirming the efficacy of this treatment in terms of local control and toxicity.

Interestingly some authors have investigated time of radiotherapy in circadian cycle, suggesting that there are no difference on failure outcomes between early morning and late afternoon radiotherapy delivery, but afternoon radiotherapy was associated with higher-grade 2-skin toxicity [46].

Patient related factors

Patient related factors have been investigated too for establishing a correlation with radiotherapy toxicity. Age and postmenopausal status seem to be correlated with a worse cosmetic outcome [47]. Large breast size women have been reported to experience acute skin reactions five times more than small breast size ones [48,50]. Body mass index is independently associated with increased risk of acute skin toxicity too [51,52].

The worst skin reactions are seen in inframammary and axillary folds, due probably to a greater self bolusing effect in these regions [52]. Racial differences too have been demonstrated to be associated with radiation dermatitis, black skin population experiencing a higher toxicity [53]. No conclusions can be drawn from existing data on the effect of smoking on RT related toxicity [51,54]. Genetic syndromes, such as Ataxia-Teleangioectasia, Fanconi anemia, etc may be associated with higher acute radio sensitivity [55].

STRATEGIES FOR PREVENTION

The high incidence of radiation-induced skin reactions has generated interest in methods for preventing and effectively treating such reactions. Although a general consensus among radiotherapy centres is lacking, it is generally agreed that the ideal method for preventing and minimizing skin reactions is moisturization of the irradiated area

Several products have been used for the prevention of radiation-induced toxicity. Topical steroids like momethasone or bethametasone were found to improve the outcome in diminishing dermatitis when compared with placebo [56,57]. Non steroidal agents, like sucralfate or aqueous crème, aloe vera and hyaluronic acid have failed to show any benefit when tested prospectively [58]. Some other nonsteroidal agents like silver sulfadiazine or calendula officinalis have shown to result in overall reduced dermatitis, even though these results were not replicated in more recent larger trials [59]. The barrier products, like Mepitel filmappears promising in reducing moist desquamation rate [60].

MANAGEMENT DURING TREATMENT

Lack of high quality evidence and disagreements regarding the optimal management of skin toxicity still remain. Skin washing with soap and water has showed significant reduction of acute erythema and desquamation 6-8 weeks after the treatment, the authors recommend mild *p*H –neutral or nonalcaline soaps [61]. An important study by Burch [62] challenged the previous assumption that products used as deodorants containing aluminum or zinc, would increase skin reaction, by demonstrating that there is no difference between metallic and nonmetallic deodorant products and no evidence in worsening skin outcomes with deodorant use [63,64]. Mepilex dressing too reduces skin erythema for dermatitis treatment [65]. Management of desquamation is also critical, especially the moist one. While the dry desquamation is not a cause of concern, the moist one should be monitored carefully and closely because it may worsen causing fever, infections, smelling, and pain. The use of saline soaks four times daily is encouraged [66-68], also moisture-retentive, barrier ointments after each saline soak.

PULMONARY TOXICITY

Lung is one of the relevant Organs at Risk (OaR) in planning radiotherapy for breast cancer. Acute and late lung toxicities have been widely described as Radiation Pneumonitis (RP) and radiation fibrosis. The acute one known as an inflammatory reaction occurring four to twelve weeks after completion of RT, while the late one is usually observed beyond six months [69].

Definition and grading of RP differs depending on the scoring system used e.g. grade 2 can be dyspnea, notinterfering with Activities Of Daily Living (ADL) according to CTCAE scoring system, meanwhile it needs medication with corticosteroids according to SWOG scale.

RP reflects the response to the activation of a rapid cascade of genetic and molecular events evolving during a subclinical time,

including loss of pneumocytes, increased capillary permeability, interstitial and alveolar edema and access of inflammatory cell into the intra-alveolar spaces [70]. These changes are observed on chest X rays or Computed Tomography (CT). This latter examination allows a better evidence of parenchymal changes and better demonstrates the changes restricted to the irradiated area. The most common findings are ground glass opacities and/or airspace consolidation [71,72]. Marks et al did not show any association between the presence or absence of radiotherapy induced pulmonary symptoms and the frequency of radiotherapy induced radiological changes [73]. Hernberg et al. reported clinical signs of suspected pneumonia in 29% of patients with radiological changes on CT, in nearly 68% these changes were more common three months after radiotherapy [74].

Many specific gene loci have been studied as responsibles of a greater susceptibility to radiation [75]. The association between single nucleotide polymorphisms in TGFβ1 gene and risk of RP was studied in patients with NSCLC. In multivariate analysis CT/CC genotypes of TGFβ1 at rs1982073:T869C were found to be associated with a lower risk of RP grades ≥ 2 (*P=0.013)* and grades ≥ 3 *(P=0.007*) respectively, compared to the TT genotype, after adjustment for Karnofsky performance status, smoking habit, pulmonary function and dosimetrical parameters [76].

Radiation induced lung injury occurs in almost 10-15 % of patients treated with adjuvant radiotherapy for breast cancer [77]. In retrospective and prospective studies the incidence of lung injury varies widely, ranging between 4.5-63 % [78-80], probably due to several biases [81]. A meta-analysis on the incidence of early lung toxicity in patients treated with a 3D conformal radiotherapy for breast cancer analyzed ten different studies and reported the overall incidence of clinical and radiological RP as 14% and 42 % respectively [82].

It is crucial to minimize radiotherapy related complications as most of the breast cancer patients are long survivors. If the incidence of symptomatic RP is reduced, not only QoL but also the compliance of breast cancer patients may be improved.

RISK FACTORS

Several risk factors for radiation induced lung injury have been studied including age, BMI, irradiated lung volume, radiation dose, central lung distance, pre-radiotherapy functional level and concurrent chemotherapy [83-87].

Patient age seems to be the strongest predicting factor for radiotherapy lung toxicity [80]. Increased age has been correlated with both clinical and radiological lung changes [85]. Many studies have suggested that patients older than 55 or 59 years have to be treated cautionary with post-operative RT [81]. Furthermore BMI have been shown by different authors to be a good indicator of the risk of pneumonitis, suggesting a low BMI to be associated with higher incidence of symptomatic RP. Conversely some other authors did not show a significant association between RP and BMI [88-91].

Smoking habits represent another baseline risk factor. Association between smoking and lung radiotherapy injury is still debated, since published studies showed conflicting results [80]. A history of smoking increases the risk of RP as a result of pre-existing lung damage, but active smoking seems to protect the lung from radiotherapy-induced damage [92].

Pre-treatment lung inflammation seems to make pulmonary tissue more susceptible to radiation damage. This hypothesis has recently been demonstrated: volumes within the lung (excluding tumour) that show an avid uptake of 18F-Deoxyglucose (FDG) before radiotherapy are more susceptible to radiation damage. Therefore, the risk of radiation-induced lung toxicity may be decreased by applying sophisticated radiotherapy techniques to spare volumes in the lung with high FDG uptake [93]. Early lung damage in patients who later develop RP can be demonstrated by an increased FDG uptake during the first two weeks of irradiation [94].

Dosimetric parameters, total dose, dose per fraction and irradiated lung volume are the main predictive factors. Despite the improvement of radiotherapy techniques and the increasing use of conformal radiation therapy radiation-induced injuries are still registrated.

Recent technique developments, such as IMRT, VMAT, helical tomotherapy, Image-Guided Radiotherapy (IGRT), breathing adapted techniques, etc have helped to optimize the dose distribution into the PTV and to reduce doses to the OAR. Concerning unconventional RT schedules, major clinical trials of hypofractionated whole breast radiotherapy have reported no significant differences in lung injury rate [95].

Reported risk of pulmonary toxicity using APBI is low and is mainly correlated with the kind of radiotherapy technique; the 3D conformal one seems to involve a slightly higher volume of lung in comparison to the others [96].

Lung is known to be very sensitive to both dose per fraction and total dose so that well defined dose parameters are standardized and used in daily practice.

Ipsilateral Mean Lung Dose (MLD) and V20 are considered the most important ones. MLD values\20 Gy and V20\20 % for the ipsilateral lung are considered acceptable in case of whole breast RT. A significant relation between V13 and radiological changes on CT images was reported [97-99]. Prone position seems to be associated with a reduction in the amount of irradiated lung [100].

Ramella et al. [101] showed that adding ipsilateral lung volume received 20 Gy (IV20) and ipsilateral lung volume received 30 Gy (IV30) to the classical total lung constraints reduced pulmonary toxicity in concurrent chemoradiation treatment. They suggested that not all beam entrances should be on the ipsilateral lung. A conservative approach would be to use the constraint settings IV20 and IV30 as simple predictive factors of lung injury. According to a recent publication IV20 is the greates risk predictor factor [102].

Goldman et al. [103] showed that minimizing the percentage of the ipsilateral lung dose to V20 < 30% can significantly reduce moderate to severe radiological changes and symptomatic pneumonitis. Lind et al. [78,85] concluded that the incidence of short-term moderate pulmonary complications in adjuvant locoregional 3Dradiotherapy for breast cancer is clinically significant. Their results also suggested an association among pulmonary complications, older age and incidentally irradiated lung volume. Another recent report suggests that utilizing multiple variables including V20 to the ipsilateral lung, age and BMI could better estimate the risk of pneumonitis [102]. Lymphnode treatment increases the irradiated lung volume and the dose to the lung. Several studies have demonstrated an increased risk of RP in case of loco-regional (breast/chest wall+lymphnodes) radiotherapy compared to brest/chest wall radiotherapy alone [104-106]. Several authors and meta-analysis have found a strong

association between supraclavicular field irradiation and incidence of RP [82]. The Internal Mammary Nodes (IMN) irradiation too is associated with an increased incidence of RP [78,85]. Another study found a strong correlation between using electrons beams for the chest wall and symptomatic RP, probably related to the inhomogeneity caused by the scattering effect of electrons [104]. Chest/Lung Distance (CLD), easy to measure at the time of simulation [107], has been shown to be predictive of lung toxiticy because of its correlation with the irradiated lung volume [108]. This paremeter gain impontance especially in case of tangential fields treatments.

The recent publication of the EORTC trial 22922-10925 results confirms that radiotherapy on lymphatic drainage improves the risk of lung fibrosis, even if in less than 5% of the population, at a median follow-up of 10 years. Only 3% of the 3866 eligible patients experienced pulmonary fibrosis (4.4% in the nodal-irradiation group vs. 1.7% in the control group, $P < 0.001$). No significant difference was observed between the two study groups with respect to performance status. The author registered an increased risk of pulmonary fibrosis at 10 years if compared with 3 year follow-up in both groups (from 0.9% to 1.7% in the control group and from 2.8% to 4.4% in the nodal-irradiation group [109].

The use of breath holding techniques even for right sided breast cancers, if lymphatic drainage radiotherapy is prescribed, lowers the risk of pneumonitis and secondary lung cancer (even in smoking patients) suggesting to apply breath-hold for locoregional irradiation of right-sided breast cancer patients [110].

Several studies concerning mortality from RT-related lung cancer showed that the risk is correlated with total dose to the lungs, thus recommending a mean dose of 7-18 Gy for the ipsilateral, and a dose of 0.1-3 Gy for the contralateral lung [114].

SYSTEMIC TREATMENT RELATED FACTORS

Many studies have shown that concomitant RT and endocrine therapy (tamoxifen) could represent a pulmonary fibrosis risk factor [111]. In patients receiving adjuvant hormonal manipulation, tamoxifen and RT is routinely associated, but should be administered with caution in case of potentially radiosensitive patients. Conversely concomitant RT and aromatase inhibitors seems to be safe and no toxicity was observed in the irradiated lung tissue [112], although estrogen deprivation has theoretically a negative effect on post-radiation tissue remodeling. Several chemotherapeutic agents are able to induce pulmonary toxicity, independently by RT. The concomitant administration of paclitaxel and RT significantly increases the risk of lung injury due to the radio-sensitizing effect of taxanes, and should be therefore avoided [113].

PREVENTION

The effect of giving a radioprotective agent concomitantly with radiation to prevent normal lung tissue toxicity is the object of research in several studies. Amifostine, an aminothiol with broad-spectrum cytoprotection, did not reduce the incidence of RP in a large randomised Phase III RTOG study. Neither there was evidence of a tumour-protecting effect [115]. Pentoxifilline taken during radiation therapy significantly decreased pulmonary toxicity in a small study [116].

Incidentally the ACE inhibitor use decreased the risk of RP in lung cancer patients receiving thoracic irradiation in a retrospective study and in animal models [117].

TREATMENT

There are no controlled, randomised trials on the treatment of RP. In case of grade I toxicity patients are mostly asymptomatic with only radiographic findings and seldom a dry cough. No treatment is recommended. In case of grade II toxicity corticosteroids are suggested if patients have more severe complaints. However, mild forms of grade II can be treated with inhalation corticosteroids and bronchodilators. More severe grade II and grade III toxicities are treated with Prednisolone 30-40 mg daily for two weeks followed by a slow dose reduction for six to twelve weeks [118]. A relapse may occur after discontinuation of corticosteroids. A substantial reduction in symptoms is normally seen, as well as an improvement of the radiological abnormalities. For patients with grade IV RP and severe respiratory insufficiency, continuous oxygen or even assisted ventilation is required. Some patients with RP are resistant to corticosteroids. This is due to more than 1.5-times increase of the lung epithelium-specific protein Krebs von den Lungen-6 (KL-6), which is produced by and secreted by type II pneumocytes. It is suggested that these patients can be treated with azathioprine or cyclosporine A [119]. There is no proven effective treatment for radiation-induced lung fibrosis. It occurs months to years after the end of RT, in response to the initial tissue injury, and leads to permanent impairment of oxygen transfer [120].

CARDIOVASCULAR TOXICITY

It is well known that postoperative radiotherapy may have adverse effects in long-term survivors and an increased mortality was observed in long-term survivors since the first meta-analysis by Cuzick and colleagues [121]. The Scandinavian studies and cancer registries identified a high rate of cardiac deaths in patients treated with post-operative RT for left sided breast cancer and underlined its role in the increased long-term mortality of this population. Interestingly a clear dose-response relationship was defined according to Scandinavian trials analysis. This dose-effect relationship has been confirmed by the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 2005 [122]. Since then, these consolidated findings have been consistently taken into account for modern radiotherapy treatment planning [123].

The exact causes of cardiotoxicity after radiotherapy in breast cancer patients is not clear [124].

The potential role of radiotherapy in causing cardiotoxicity derives from the evidence that patients, treated with mantle field irradiation for Hodgkin lymphoma, experienced pericarditis, as well as congestive heart failure, ischemic coronary artery disease, arytmia or miocardial infarction [125].

Experimental evidence suggests indirect harmful effects of microvascular and macrovascular damage on the myocytes. It has been postulated that radiotherapy leads to an acute inflammation within the heart blood capillaries and to continuous inflammatory processes, resulting in endothelial cell proliferation and formation of fibrin thrombi with obstruction of the myocardial capillary lumen. A consequently reduction of collateral flow and vascular reserve causes ischemia and macrovascular injury. This phenomena could accelerate an age related atheroschlerosis leading to CAD (Coronary Artery Disease) [126]. Therefore, it is quite comprehensible that epidemiologic studies detected baseline cardiac risk factors as independent risk factor for cardiovascular disease after radiotherapy. Those risk factors are age, hypertension, diabetes mellitus, high

total cholesterol levels, family history of early myocardial infarction and smoking [127]. Concomitant administration of cardio-toxic systemic treatments should be strongly considered when prescribing RT. Cardiotoxicity of anthracycline-based chemotherapy regimens is well-known and studied; therefore their concomitant use with radiotherapy is not recommended. Safety of adding trastuzumab to standard adjuvant systemic therapy for Human Epidermal Growth Receptor 2 Factor (HER2) positive early breast cancer was largely demonstrated [128]. Among patients who received radioherapy, there were no significant differences across treatment arms in the incidence of acute skin reaction, pneumonitis, dyspnea, cough, dysphagia, or neutropenia. In particular, the 3-year cumulative incidence of cardiac events was 2.7 % with or without radiotherapy. Safety of trastuzumab, given concomitantly to radiotherapy in the adjuvant setting, was further investigated in large observational serie and no significant impact on cardiac toxicity profile was detected [129,130].

Asian studies have demonstrated, on the contrary, a higher risk of acute LVEF dysfunction [131] suggesting that trastuzumab and left sided radiotherapy have at least a combined effect on cardiac toxicity. The authors suggest that a LVEF > 50% before the initiation of trastuzumab and RT is required. The main limitation of this study is that LVEF is not sensitive enought to detect early and minor cardiac disfunction, so that the actual toxicity might be underestimated [131].

The cardiac toxicity of radiotherapy in breast cancer is certainly less than the one of several drug therapies. However, up to now, it still remains unclear if late effects after combination of both therapies can become manifest in old age with decreasing compensation ability of the heart. Finally, this is not a specific radiotherapy related toxicity but a multifactorial one [132]. Several studies deal with the effect of dose on specific cardiac structures in patients undergoing radiotherapy. Lind et al. [133] evaluated post-radiation regional myocardial heart perfusion changes with Single-Photon Emission Tomography (SPECT) in 69 patients. They correlated the Left Anterior Descending artery (LAD) distribution SPECT changes with the percentage of irradiated Left Ventricle (LV) volume and risk factors for coronary artery disease. The meta-analysis of Darby et al. [134] confirms well-known data on cardiac risks in old studies and has identified a dose-response relationship. Unfortunately it gives no conclusive answers to the most important question of how best to protect the heart against radiation toxicity. CAD rate increased linearly with the mean dose to the heart, with no apparent threshold. Critical doses and volume relationships are not well defined, mainly due to wide variation in structures delineation [135]. Current recommended mean heart dose is around 2-7 Gy for left-sided, and 1.5 Gy for right-sided patients [136]. Despite a significant reduction in the mean heart dose has been observed in the last decades with the development of more sophisticated raditherapy techniques, an increased risk of cardiac toxicity has been registered [137].

Due to this reason national and international guidelines highlight the sparing of the Organs at Risk (OaR), with peculiar attention to the heart. The Danish Breast Cancer Cooperative Group suggests to administer the prescribed therapeutic dose to the tumor bed sparing LAD, heart and lung [138]. The authors suggest, in case of standard treatments, to respect the following dose constrains: for LAD maximum 20 Gy, for heart V20\10 %, and V40\5 %, using standard fractionation.

Hypofractionation for whole breast RT is approved, recommended, increasingly used and often considered a standard treatment schedule [139]. No evidence of a higher incidence of adverse cardiac events is reported, and some authors suggest that hypofractionated RT might be even safer, in terms of heart sparing, than conventional regimens [140]. An innovative fractionation schedule (hypofractionation with integrated boost) was tested, and doses to organs at risk were routinely determined and documented during treatment planning. Interestingly the mean heart dose was only 1.48 + 0.9 Gy *(n=151)* [141].

The IMN irradiation is associated with an increased dose delivered to heart and coronary artery. The EORTC 22922-10925 study results showed that, after 10 years of follow up, 1% of patients had cardiac fibrosis (1.2% if lymphnodes RT vs. 0.6%, $P = 0.06$), and 6% had cardiac disease (6.5% if lymphnodes RT vs. 5.6%, $p = 0.25$) [109].

On the contrary, no increased rate of cardiac disease was observed in the nodal-irradiation group of the Canadian trial at a median follow up of 10 years [142,143].

The Danish Population-Based Cohort Study evaluated 3089 patients on the effect of internal mammary node irradiation in early node-positive breast cancer. The authors registered equal numbers of patients who died of ischemic heart disease in both groups with a median follow-up of 8 years [144].

PREVENTION

Innovative techniques have been tested for avoiding inappropriate high doses to heart and LAD. Conventional 3DCRT uses tangential beams toavoid high dose region in the Ipsilateral Lung (IL) and heart. However, it results in poor conformity, homogeneity and hotspots outside the target volume. On the other hand Intensity Modulated Radiotherapy (IMRT) and Volumetric Arc radiotherapy (VMAT) improve the dose conformity inside the target at the cost of an increased low dose spread to Contralateral Lung (CL) and Contralateral Breast (CB) which could increase the risk of secondary cancer [145,146]. Additional advantages of these techniques is their ability to provide differential dose distributions, allowing the Simultaneous Integrated Boost (SIB) delivery [147,148] Of note IMRT plans employ higher Monitor Units (MU) and hence increases the delivery time by 3-4 folds compared to VMAT and conventional 3DCRT. Increase in treatment time, MU, leakage, scatter radiation in IMRT has implications on tumor cell repair and repopulation [149,150].

Another issue of post-operative radiotherapy is the breast motion due to breathing. At present, the Deep Inspiration Breath Hold Technique (DIBH) is increasingly used for reducing the target motion and primarily for reducing the hearth dose [151-153]. In deep inspiration, the heart sinks down and the distance from the chest wall increases. First dosimetric studies on single patients showed a significant reduction in heart and lung dose using this modality. It has to be clarified whether the unique dosimetric advantage is clinically relevant or not, as of today there are no prospective studies or data demonstrating a possible clinical benefit of DIBH irradiation on the late cardiac toxicity rate for left breast irradiation. Noteworthy preliminary retrospective data on CT based “calcium score” of the coronary arteries provided some evidence that radiotherapy of left sided breast cancer using breath hold may be associated with less calcification [154]. Due to the long interval between radiotherapy and the appearance of heart toxicity, we need many years to assess the clinical impact of DIBH on cardiac toxicity. Even though the best clinical practice is to reduce the heart and LAD dose to as low

as reasonably achievable. Data from the major retrospective series indicate that an increasing mean cardiac dose was clearly associated with a proportional increased rate of major coronary events [155,156]. Sardaro et al. reported a 4% increase in the late heart disease risk per 1 Gy in mean heart dose [156]. Darby et al. have estimated that a 1 Gy increase in mean heart dose will result in a 7.4% higher rate of major coronary events, defined as myocardial infarction and death from ischemic heart disease [155]. Obviously, mean heart dose sufficiently reflectes coronary artery exposure in patients treated with DIBH in a recent analysis [157,158].

A recent study [159] showed a significant reduction in mean heart dose of 20% with IMRT and 23% with VMAT. (In this study also was seen an additional decrease in heart and LADCA dose by IMRT in both FB and DIBH irradiation, compared with VMAT) Therefore, it has been ongoing and continuing institutional policy to use the DIBH technique whenever feasible as the standard irradiation method for all left-sided breast cancer patients in order to keep the heart and LAD dose as low as possible.

Irradiation in prone position is another promising treatment option. Several publications are in favor of replacing the supine standard position by the prone one for whole-breast irradiation, especially in patients with large breasts [160-162]. Recently, Mulliez et al. [160] reported a phase III randomized trial in this context, in which skin desquamation, dermatitis and edema were significantly reduced. Moreover the dose to the ipsilateral lung and the LAD were significantly reduced. Comparing the prone and supine treatment positions in 400 patients, Formenti et al. [162] evaluated the in field volumes of the heart receiving the full dose as a surrogate for normal-tissue exposure. They described a considerable anatomical variability of the volume range, but were also able to show a significantly lower mean dose to the heart in the prone position.

Another way to reduce heart toxicity should be the use of Accelerated Partial Breast Irradiation (APBI), which exclusively targets only the lumpectomy site plus some margin. Current techniques for APBI are Intraoperative Radiotherapy (IORT), multi-interstitial brachytherapy, intracavitary brachytherapy and external beam radiotherapy. The available data on APBI suggests acceptable local control and survival in selected patients with low-risk breast cancer [163].

THYROID TOXICITY

The true prevalence of radiotherapy-induced Hypothyroidism (HT) in patients who receive radiotherapy is not known because Thyroid Function Tests (TFT) are not routinely assessed prior and after the treatment. Additionally, the radiation dose to the thyroid gland is not routinely evaluated because this organ is neglected as OaR, especially if only the breast is irradiated [164].

HT is one of the late toxicities of curative RT to the neck region, and the reported incidences of HT ranges from 20% to 52% in patients treated with radiotherapy for head and neck cancers and Hodgking disease [165-168].

Conversely only few studies have performed clinical DVH analysis for thyroid dysfunction after radiotherapy in breast cancer patients and, according to their results, the incidence of HT varies from 6% to 21% [169-173].

Thyroid dysfunction develops in nearly 15% of patients, it is detectable usually 3 months after the end of radiotherapy and progressively increases at nearly 6 years from the end of radiotherapy, the authors registered the maximum amount of HT in nearly 66% of patients [174-177]. Therefore they considered this toxicity as a late side effect of radiotherapy. The cumulative incidences [178] of HT in patients irradiated in the supraclavicular region at 3, 4, and 5 years after treatment were 10%, 22%, and 40%, respectively, whereas the cumulative incidences of HT in patients not irradiated in the supraclavicular region at 2, 3, and 5 years after RT were 3%, 8%, and 27%, respectively.

HT can be easily diagnosed with laboratory tests, including serum Free Thyroxin (FT4), Free Triiodothyronine (FT3) and Thyrotropin (TSH). Clinically evident HT is generally characterized as a reduction in serum FT4 concentration with a high serum TSH concentration and the existence of clinical symptoms like fatigue/weakness, weight gain, cognitive dysfunction, edema, cold intolerance, myalgia/paresthesia, depression, decreased hearing, constipation, dry skin, arthralgia, menorrhagia, and hoarseness. In the subclinical HT, on the contrary, the patients have no sympthoms but increased TSH concentration while FT4 level could be low or within normal limits.

Radiotherapy induced hypothyroidism is caused by the damage of small thyroid vessels and artheriosclerosis of larger vessels, additionally parenchymal injury of thyroid cells and secondary capsular fibrosis contribute toimprove toxicity [179].

The irradiation dose is a significant factor for the prediction of thyroid dysfunction [180-184] but, as previously stated, few researchers consider routinely thyroid as OaR and evaluate the Dose Volume Hystogram (DVH) of this organ. Kuten et al underlined a correlation between the dose to the tyrhoid and HT [185]. Yoden et al. [186] too analysed DVHs to evaluate the correlation between the percentage volume of the thyroid gland receiving doses and the thyroid function. These researchers have suggested that the percentage volume of the thyroid gland receiving doses between 10 and 60 Gy (V10 to V60) would represent a predictor of HT, and the percentage volume of the thyroid gland receiving doses V10 to V30 had a significant impact on the peak level of TSH. Similarly, Cella et al. [182] showed that the V30 value was the only predictor for HT. Additionally, Akgun et al. [181] reported that V30 was a statistically significant predictor for the development of HT. Kim, et al. [183] revealed that the thyroid V45 value can predict the development of HT and a V45 of 50% can be used as a threshold in RT planning. In contrast, Diaz et al. [187] reported no clear correlation between Dmean, Dmin, Dmax, V10 to V70 and HT. These data are confirmed by Alterio et al: in their experience too Dmean, Dmin, Dmax, V10, V30, V50, and 5 other point doses were not associated with HT [168]. In the study by Johansen et al. [173] 15 patients with small thyroid volumes experienced a higher risk to develop HT after RT, as less thyroid tissue receiving doses less than 30 Gy is available for adequate thyroxin making; anyway in their study no statistically significant intergroup variations were found between V20 and V50. According to the study published recently by Kanyilmaz G.et al. [178] HT group had smaller thyroid gland volume than those with normally functioning glands (13.25 cm^3 vs 19.63 cm^3, respectively, $p = 0.08$), but the results were not significant. There were no relationships observed between Dmin or V10 to V50 and HT, but Dmean and Dmax were statistically significant dosimetric predictors for HT. According to multivariate regression analysis, Dmean was the only prognostic factor that predicted HT. The authors concluded that Dmean > 21 Gy was a threshold value for the development of HT.

Some others risk factors were identified as predictors for thyroid disfunction. Radiotherapy volumes are statistically significant predictors in the study of Kanyilmaz et al. [178] 84 % of patients with HT were in the supraclavicular region irradiated group. Smith at al. [171] found no difference in the incidence of HT between breast cancer patients with more than 4 positive lymphnodes and therefore irradiated on the supraclavicular fossa if compared with patients treated on the breast/chest wall only.

Age is associated with the development of postradiation HT. Radiosensitivity of the thyroid gland is believed to decrease with increasing age [171,187] even if in the cohort of Kanyilmaz G, et al. [178] age did not have a statistically significant effect on HT.

Chemotherapy impact on HT is not clearly proven. According to Jereczek-Fossa, et al.'s review [179], the impact of chemotherapy and hormone therapies on the risk of HT was controversial. In Kanyilmaz et al. hemotherapy administration was not a statistically significant predictor of HT [178]. Hormonotherapy too has no impact on the risk of HT. This study confirmed that the extent of surgery and the nodal status, related with supraclavicular fossa irradiation, were also a statistically significan predictor for HT.

Prevention and treatment: The practice of nodal radiotherapy for early breast cancer is increasing in many centres. Sentinel node biopsy is now standard practice and there is a move towards considering radiotherapy instead of further surgery for some lymph node positive patients. This policies derive particularly from the results of the EORTC 10891-22023/ AMAROS trial which showed very low recurrence rates in the axilla with radiotherapy and surgery [188].

The EORTC trial 22922/10925 investigated 4004 patients for detecting the role of lymphnode irradiationin low-inermediate risk breast cancer patients [142]. They report that disease-free, distant disease-free survival and breast-cancer mortality were improved and a marginal effect on overall survival was detected in the group of patients irradiated on the regional lymphnode volumes. The Canadian MA20 study reported on 1832 women who were node positive or high-risk node negative following conservative breast surgery and either an axillary dissection or sentinel-lymph-node biopsy [143]. They report that the addition of regional nodal irradiation did not improve overall survival but reduced the rate of breast-cancer recurrence.

Both these trials have lead conseguently to an increased rate of irradiation of regional lymphnodes in breast cancer patiens. The technology improvement of radiation therapy surely allows a better dosimetric coverage of the lymphnodes PTV with the possibility to erogate a lower dose to the OaR.

This dose coverage was greatly improved for plans produced with modulated techniques, saving in this way as much as possible the thyroid gland.

Clinical HT is an irreversible condition, requiring lifelong treatment with thyroxin supplementation. Replacement treatment reverses all symptoms and signs of HT [180]. However, if replacement treatment is not carried out, both clinical and subclinical HT are related to worse perception of quality of life.

According to the American Association of Clinical Endocrinologists and the American Thyroid Association Guideline for HT [189] patients who had clinical or subclinical HT with elevated serum TSH concentration above 10 μU/mL were planned to require hormon replacement therapy.

BRACHIAL PLEXUS TOXICITY

Neurological symptoms and signs of brachial plexus dysfunction may occur as a complication of radiotherapy for the treatment of breast carcinoma, but may also result from metastatic spread of tumour, unrelated acute brachial neuritis, traumato the plexus during surgery or radiation-induced plexus tumours. The most common causes are Metastatic Brachial Plexopathy (MBP) and Radiation-Induced Brachial Plexopathy (RBP).

The wider indications to adjuvant radiotherapy on regional lymph nodes and specifically on suvraclavicular fossa highlight the risk of improved neurological toxicity caused by the unavoidable irradiation of the brachial plexus [142,143]. The recent publication of the results of the EORTC 22922/19025-MA20 and Danish trials indicates that locoregional radiotherapy has an impact on DFS, DMFS andOS, even not significative with a median FU of ten years. This benefit is detected even in patients with 1-3 positive axillary lymphnodes [190-193].

The timing to onset of brachial plexopathy and the first symptom of plexus disorder variy widely. The average interval rangesbetween 7.5 months tand 6 years while symptoms may develop decades after treatmet or with a relatively short latency as indicated by other authors [194-198]. Kori et al reported that symptoms from brachial plexopathy arose within 4 years from treatment [194], while Fathers et al. reported that the median time to onset of symptoms was 1.5 years [196]. The median follow-up time since RT completion was over 5.5 years in the report of Leong et al. [199] enough to identify arm morbidity, including plexopathy-associated symptoms and functional deficits, if present.

Conversely we will have to consider that several previous studies, in which larger doses per fraction was prescribed, demonstrated a latency period up to 20 years [195,197,198].

The mechanism of plexophaty is believed to be a combination of failure of cellular proliferation and localized ischemia. The net result is fibrosis of the neural and perineural soft tissues secondary to microvascular insufficiency. This, in turn, leads to ischemic damage to the axons and Schwann cells [200].

Sensory symptoms, such as numbness, paresthesia and dysesthesia, swelling and weakness of the arm are the predominant clinical evidence of such a damage. These neurologic symptoms can be progressive and may lead to a weak and edematous arm.

Most radiation plexopathies are painless, but when present, pain symptoms are usually limited to the shoulder and proximal arm. Such pain usually is rated as mild to moderate in intensity. Significant pain complaints are more commonly associated with recurrent tumor than with radiation plexopathy [200].

The frequency of radiation-induced brachial plexopathy has declined over the past 60 years and depends significantly on both the radiation dose and the proximity of the radiation volume to the underlying plexus. In the 1950s, the incidence was as high as 66% after 60-Gy total dose to the axilla and supraclavicular area using 5 Gy/fraction. The current incidence is 1-2% in patients receiving a typical dose of less than 55 Gy [201].

Breast carcinoma accounts for 40-75% of reported cases of brachial plexophaty, followed by lung carcinoma and lymphoma [194-196].

Paresthesia is a fairly common sympton among women treated with post-operative radiotherapy for breast cancer in Sweden, with a prevalence of approximately 17% [202].

Lundstedt et al reported 25% of paresthesia after RT of supraclavicular lymphnodes, 13% in patients without RT [203].

RISK FACTORS

The radiation dose, treatment technique, concomitant use of chemotherapy, surgical lymph node dissection and underlying comorbidities such as diabetes, hypertension, obesity, and vascular disease have been demonstrated significant association with the development of radiation injury to the brachial plexus [204,205].

Given that breast cancer often is treated with radiation therapy, women experience a greater incidence and prevalence of radiation-induced brachial plexopathy than men [206].

Advanced age may be a risk factor for the development of brachial plexopathy after radiation treatment [207].

It is well known that high doses to the brachial plexus increase the risk of neuropathy, as shown by Powell, et al [208], Olsen, et al [209] and Johansson, et al [195] in their comparisons of different fractionation schedules.

The effects of nodal RT total dose and dose per fraction on the risk of brachial plexopathy have been evaluated in studies conducted before the era of CT planning. In a retrospective study of 449 patients treated from 1982-1984, Powell et al reported that symptoms of brachial plexopathy increased from 1% with 54 Gy in 30 fractions (1.8 Gy/fx) to 6% with 45 Gy in 15 fx (3 Gy/fx). *($p = 0.09$)* [208].

Galecki et al. suggested that the rate of radiation induced plexophaty increased sharply with doses beyond 55 Gy (delivered at 2 Gy/fx) [206].

As shown in a recent publication by Leong et al. [199], limiting hypofractionation to fraction sizes 2.25 to 2.5 Gy/day with a compensatory reduction in total dose may reduce overall treatment time, without increasing the risk of shoulder or brachial plexus fibrosis. In the UK Standardisation of Breast Radiotherapy (START) A and B trials, nodal radiotherapy was prescribed in 14% and 7% of subjects respectively [210]. Hypofractionation in the START trials was not associated with increased risks of arm symptoms, brachial plexopathy or lymphedema [210]. The START A trial reported one case of brachial plexopathy (0.1%) if a schedule of 41.6 Gy in 13 fractions (3.2Gy/fx) was used. The START B trial reported no case of plexopathy among 82 women treated with 40 Gy in 15 fractions (2.67 Gy/fx). These findings were confirmed by a retrospective series of 257 patients treated with HFRT 42 Gy in 15 fx (2.8Gy/fx) which reported no cases with brachial plexopathy with a median follow-up of 6 year [211].

Another randomized trial [212] reinforce these data. In the British Columbia post-mastectomy RT (PMRT) randomized trial [213], locoregional radiotherapy was delivered over 16 fractions in which the mid-axillary dose was 35 Gy, a dose lower than the HF nodal RT prescriptions evaluated in the current study. The short PMRT regimen resulted in a significant reductions in the risk of loco-regional recurrence and improvements in 20-year breast cancer survival. Although limited by cross-trial comparison, the locoregional control and survival outcomes observed in the British Columbia trial were consistent with outcomes in the Danish PMRT trial in which a conventiona fractionation was used. In a recent study published by Nelson Leong, et al. [199], hypofractionation was not associated with increased patient reported arm symptoms or functional deficits compared to conventional one.

In the report by Lundstedt, et al. [203] paresthesia in relation to dose/volume was evaluated. Paresthesia was reported in 25% of patients treated with raditherapy to the supraclavicular lymphnodes, with a V40Gy ≥ 13.5cm^3, compared with 13% if no radiotherapy was prerscribed, RR1.83 (95% CI 1.13-2.95).

A irradiated volume effect was suggested by Emami, et al [214] when they irradiated the brachial plexus by thirds: radiotherapy on one third induced less toxicity probably because one third was a little more radio-resistant than all 3 at the same time. Volume effects after irradiation of the brachial plexus has also been suggested by Amini et al [215] and Eblan et al [216].

REHABILITATION PROGRAM

Therapeutic modalities should focus on reducing pain, strengthening, preservation of range of motion and limiting lymphedema. The interventions and modalities stricly depend on the kind of impairments (i.e. weakness, pain, lymphedema, range of motion) and are based on occupational therapy and sensorial/motorial re-education techniques [217]. Anticonvulsants and antidepressants are used to manage severe muscle spasms and provide pain relief in neuralgia.

PROGNOSIS

One third of patients experience severe progression of their radiation-induced plexopathy, whereas the remainder a gradual one. A mild form of reversible radiation plexopathy may present rarely.

PATIENT EDUCATION

Patients should be awared on the expected progressive course of radiation plexopathy. A home exercise program should be considered to preserve strength and range of motion of shoulder and arm. Susceptibility to trauma and infection due to altered sensation, edema and fibrotic tissue should be discussed.

RARE TOXICITY AND SECONDARY TUMORS

The risk of secondary malignancies has been analysed by the Danish Breast Cancer Collaborative Group: 18% of the pre-menopausal breast cancer patients treated with surgery alone developed a second non breast cancer: ovarian, endometrial and biliar tract cancer were the most frequent ones [218].

The annual risk ratio of radio-induced secondary cancer is 1.2, increases with follow up and is strictly correlated with the age at radiation treatment [219].

Two SEER studies evidenced no increased risk of secondary cancer in breast cancer patients treated with radiotherapy in the volumes receiving if < 1Gy, while the risk increased if dose overcame 1 Gy in organs such as pleura, esophagus, lung, bone, soft tissue and contralateral breast. Only 5% of controlateral tumors and 6% of the other cancers could be correlated to the previous radiation treatment in a population of 182000 women [220,221].

The risk of radio-induced sarcoma is nearly 0.2% at 10 years, tipically are induced by high doses and so arise usually inside the irradiated volumes. In case of angiosarcoma the interval should be lower, between1 and 2.5 years from the end of radiotherapy [222].

The risk of controlateral breast cancer depends on several factors (hormonal, genetics) while radiotherapy seems to have a role in improving the risk only in young women if irradiated on the internal breast quadrants [223].

A slightly improvement of lung cancer has been detected if high volume of lung has been irradiatiated especially in smokers patients and if high lung volumes have been irradiated [224,225].

CONCLUSIONS

Radiation side effects have been extensively analyzed and categorized usig international scales (EORTC/RTOG, NCI CTCAE). The prevention and treatment of the most frequent radiotherapy toxicities are nowadays better standardized, due to technical improvement and dedicated personnel (phisicians, nurses, radiographers). Conversely we lack clear data on the interaction between radiotherapy and the other specific treatments (i.e. chemo/hormono/immunotherapy, surgery, reconstructive surgery) and their best sequences for reducing toxicity. Moreover, due to recent publications, we will have to consider the irradiation of regional lymphnodes even in intermediate risk patients. This new attitude enforce more attention to neglected toxicities, such as the thyroid and brachial plexus ones, especially in these long term survival patients.

The patients characteristics have to be taken into account too for prescribing a tailored radiotherapy with the lowest collateral effects and toxicities.

Technological improvements allow us to obtain more dedicated treatments, image guided radiotherapy assures a proper positioning of the patients during the treatment and the respiratory gating allows a reduced dose to the hearth and the anterior coronary artery.

We aim that a wider diffusion of these new tools will further decrease acute and late radiotherapy toxicity.

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