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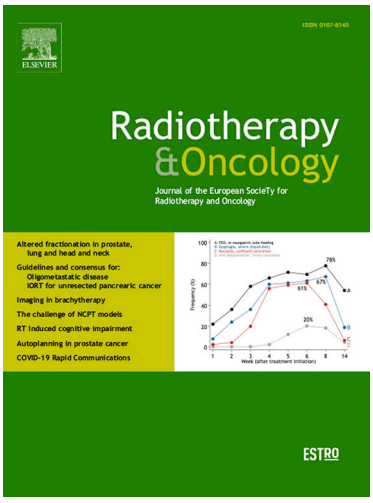

Original Article

A Delphi study and International Consensus Recommendations: The use of bolus in the setting of postmastectomy radiation therapy for early breast cancer

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A Delphi study and International Consensus Recommendations:

The use of bolus in the setting of postmastectomy radiation therapy for early breast cancer

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RUNNING TITLE: Consensus recommendations on the use of bolus in post-mastectomy radiation therapy

KEY WORDS: breast cancer; mastectomy; radiation therapy; post-mastectomy; PMRT; bolus; tissue compensator.

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Abstract

Bolus serves as a tissue equivalent material that shifts the 95-100% isodose line towards the skin and subcutaneous tissue. The need for bolus for all breast cancer patients planned for postmastectomy radiation therapy (PMRT) has been questioned. The work was initiated by the faculty of the European SocieTy for Radiotherapy & Oncology (ESTRO) breast cancer courses and represents a multidisciplinary international breast cancer expert collaboration to optimize PMRT. Due to the lack of randomised trials evaluating the benefits of bolus, we designed a stepwise project to evaluate the existing evidence about the use of bolus in the setting of PMRT to achieve an international consensus for the indications of bolus in PMRT, based on the Delphi method.

Introduction

Up to the late nineties, most departments used Cobalt-60 (Co-60) Units for radiation therapy (RT) for superficially located indications, including postmastectomy RT (PMRT) for early breast cancer. With the transition to linear accelerator photon-based RT, bolus material was often added to allow for a similar surface dose distribution as received with the Co-60 machines due to the skin sparing effect of photons [1]. Bolus serves as a tissue equivalent material that shifts the 95-100% isodose towards the skin and subcutaneous tissue (depending on the thickness of bolus and subcutaneous tissue) [1]. The need for bolus for all breast cancer patients planned for PMRT has been questioned due to skin toxicity as seen in a number of studies [2-20], clinician surveys [21-25], and national guidelines [26]. All studies showed huge variability in terms of bolus indications and use, with no proven optimum regimen pertaining to thickness, schedule (i.e., daily, alternating days), bolus material, and RT planning characteristics (such as beam energy) [1-20]. Unfortunately, the use of bolus was not evident from large, randomized trials that led to significant changes in radiation oncology practice, since they failed to address

the utilization of bolus in PMRT. For example, in the Danish Breast Cancer Group (DBCG) 82b&c PMRT trials conducted between 1982 and 1990 that pioneered RT quality assurance and defined RT volumes for PMRT planning, most patients were treated with electrons, but the protocol guidelines in case of photon-based planning included a wax bolus of unspecified thickness applied to the scar with a 3-cm margin cranial and caudal to the scar [27]. That strategy was guided by the pattern of local recurrences, which were by far most often detected close to the scar. Although bolus was addressed in the protocol, its technique was not audited, and whether the recommended protocol was adhered to is not indicated in the quality assurance publication [27]. As PMRT in early years was associated with significant morbidity, PMRT was commonly applied for patients with more advanced disease [28]. However, the 2005 and 2014 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) publications found PMRT to improve locoregional control at 10 years and reduce 20-year breast cancer mortality over mastectomy and axillary clearance alone in patients with less advanced disease, including with tumours less than 5 cm or with 1 to 3 positive lymph nodes, leading to the recommendation to consider PMRT also in this subset of patients [29, 30]. As a result of these findings and the omission of axillary lymph node dissection in low burden axillary disease, more patients who undergo mastectomy are now treated with PMRT [31]. Seeking to improve the outcome of patients and support the everyday practice to balance the gain from PMRT and reduce treatment-related toxicities, we revisited the use of bolus in the setting of modern PMRT to achieve a consensus for its use.

The work was initiated by the faculty of the European SocieTy for Radiotherapy & Oncology (ESTRO) breast cancer courses and represents a multidisciplinary international breast cancer expert collaboration to optimize PMRT. Due to the lack of randomised trials evaluating the benefits of bolus, we designed a stepwise project to evaluate existing evidence about the use of bolus in the setting of PMRT, its effect on local recurrences, and related toxicity. One of the

initial steps of this project was a systematic review of the literature that is published in a separate paper [32]. The aim of the current paper is to achieve consensus on the use of bolus using a Delphi process.

Material and methods

Consensus formation

A Delphi process was used to establish consensus about the use of bolus in the setting of PMRT [33, 34]. The process included a structured workflow based on Delphi process recommendations. The core clinical and RT planning group [OKP, HD, LB, DdR, PJ, IM, HN, SH, LM, PHP, BVO] planned the workflow (appendix 1). The aim of the core group was to jointly define the project, survey content, timeline, and to advise at different stages of the process. The surveys were conducted using Google Docs. In all steps of the work, the participants were encouraged to comment in free text to allow for further discussion and to retrieve arguments and evidence to support or negate a certain perspective. Prior to the project, we performed a systematic review for clinical outcomes of the use of bolus in the PMRT setting to provide evidence for its use and a physics review for better understanding physical considerations with its use in modern RT. The clinical systematic review was provided after the first survey and the physics review after the second survey. Two investigators (HD and OKP) consolidated all survey results and comments from the systematic review to form the second and third round of the Delphi process. The third survey integrated the items identified in the first two surveys, the systematic review, and the physics review into different categories based on agreement, and participants were asked to score each item on a 5-point Likert scale (1 - Strongly disagree; 2 - Mildly disagree; 3 - Undecided; 4 - Mildly agree; 5 - Strongly agree). We added statements that were aimed to form the consensus document. We generated a consensus for the use of bolus in the setting of PMRT by combining all items that reached

consensus: if ≥75% of respondents agreed mildly (4) or strongly (5), this qualified as a consensus for; and if ≥75% of respondents disagreed mildly (2) or strongly (1), this qualified as a consensus against.

Results and discussion

Panellists' survey results are available in the appendices 2 and 3. Consensus statements are presented below, including the distribution of Likert scale votes [mode, median, interquartile range (IQR)], supporting experts' opinions and scientific evidence, and decisive remarks.

1. General consensus statements

1.1 The panel *disagrees* that there is sufficient evidence to support that bolus increases local control in all patients who are undergoing PMRT.

(*statement for all types of mastectomies, without/with immediate reconstruction).

[Mode 1; median 1; IQR 1-2].

This statement is based on the systematic review summary conducted as part of this project and a recent large study published by Nichol and colleagues [6]. The use of bolus was associated with similar local recurrence rates (3.5% with bolus vs. 3.6% without) when compared to PMRT without bolus for studies included in the systematic review and was supported by three comparative studies, with no significant difference in local recurrence risk factors between treatment groups [2, 4, 5].

Panellists' comments: Bolus is indicated in selected cases, discussed below.

1.2 The panel *agrees* that the use of bolus increases the skin toxicity associated with PMRT.

(*statement for all types of mastectomies, without/with immediate reconstruction).

[Mode 5; median 5; IQR 5-5]

Based on the systematic review summary conducted as part of this project, the use of bolus was associated with clinically significant acute skin toxicity. Pooled analysis results showed that the rate of grade 3 radiation dermatitis as per the Common Terminology Criteria for Adverse Effects v3.0/4.0 (CTCAE) or Radiation Therapy Oncology Group (RTOG) was 9.6% with the use of bolus and 1.2% without [32]. Acute skin toxicity in the bolus group was associated with higher rate of treatment breaks (38% vs 6%) and early cessation of radiation (12% vs. 4%) which were associated with higher local recurrence rates in two studies [2, 5]. Other factors contributing to acute skin toxicities included older age [2], smoking [35], and systemic treatments [2]. Severe acute reactions were associated with an increased rate of telangiectasia and late toxicity (consequential late effects) [36]. Little is known about skin and subcutis toxicities associated with bolus and outcomes of immediate reconstruction.

Panellists' comments: Decisions about bolus use should attempt to balance potential benefit and harm, considering other factors known to be related to toxicity. Meticulous RT planning is important to reduce the risk of RT-related toxicity, including accounting for dose homogeneity, beam energy, electron vs. photons, dose and fractionation. The St. Gallen 2021 report [37] favours moderately hypo-fractionated regimens (e.g., 2.65-2.67, 15-16 fractions) for PMRT including in cases of immediate reconstruction, which have lower skin toxicity compared to conventional regimens (e.g., 1.8-2 Gy fractions, 25-28 fractions) and equivalent disease outcome. [37-40]

<u>1.3</u> The panel *disagrees* that bolus should be routinely used for all PMRT, regardless of patient/tumour factors and whether or not reconstruction was done prior to radiation.

[Mode 1; median 1; IQR 1-1]

Based on data provided above & below.

Panellists' comments: Bolus is indicated in selected cases, discussed below.

1.4 The panel *disagrees* that bolus should be used for all PMRT without reconstruction.

[Mode 1; median 1; IQR 1-2]

In some practices bolus is applied in case of chest-wall irradiation and only in selected cases of immediate breast reconstruction [24]. The argument is that the chest-wall, which is often thin in some areas (< 5mm), experiences more skin-sparing effects of MV photon RT compared to a reconstructed breast, which is shaped similarly to the native breast.

As indicated in the ESTRO target volume delineation for elective radiation therapy of early-stage breast cancer consensus guidelines [41, 42], the chest-wall skin is not part of the clinical target volume (CTV_p) unless there is evidence for skin involvement (T4b, c, d tumours). Moreover, in case of non-skin-sparing mastectomies, part of the breast skin together with subcutaneous tissue is resected. Data provided by the physics team for this project indicated that most treatment planning algorithms have a satisfactory agreement between measured and calculated doses observed 3-4 mm below the surface, which is per ESTRO guidelines the clinical target volume of interest in most cases of chest-wall PMRT [43-45]. Inaccuracy of measurements in these volumes might be also related to the beam energy, type (electron, photon), chest-wall separation, and beam angles. Therefore, the tangential techniques may provide sufficient dose coverage even for a thin chest-wall, therefore a thin chest-wall is not a sole indication for bolus.

Panellists' comments: After mastectomy, the primary tumour is removed, and the anatomy is altered. Determining which skin now overlies the previous "area of the primary tumour" is usually impossible. However, in cases with high risk of skin involvement where the area of the primary tumour is not fully covered by 95-100%, a bolus should be applied. Size/shape of bolus is decided on an individual basis and accounts for the high-risk volumes.

2. Indications for the use of bolus.

2.1 The panel *agrees* that bolus should be used in case of mastectomy for DCIS with positive anterior margin without overlying skin removed.

(*statement for all types of mastectomies, without/with immediate reconstruction)

[Mode 4; median 4; IQR 4-5]

DCIS is a non-invasive neoplasia; therefore, it is not expected to invade the subcutis, dermal lymphatics or skin. The mastectomy superficial margin is usually not reported [46, 47]. However, due to incomplete resection of the glandular tissue or as a result of the normal breast glands "sawtooth" extensions into the subcutis, DCIS may be present at the anterior margins or in case of nipple sparing mastectomy (NSM), DCIS may even be present as a skip lesion in the ducts in the nipple core [48-53]. Additionally, extensive intraductal component-positive carcinomas were shown to be associated with an increased risk of local recurrence when the surgical margins were not evaluated (e.g., anterior margin) or focally involved [46, 53-56]. Over 90% of all local recurrence after mastectomy for pure DCIS were invasive cancer and re-excision showed residual breast glandular tissue in addition to the lesion [54, 56-58].

Panellists' comments: Preoperative imaging can assist in estimating the extent of disease and proximity to the subcutis to plan the surgical procedure. If re-excision of the anterior margins is not feasible for pure DCIS, bolus is recommended to ensure that the area is covered by at least 95-100% of the prescribed dose.

2.2 The panel *agrees* that bolus should be used in case of mastectomy for invasive cancer with positive anterior margin without overlying skin removed.

(*statement for all types of mastectomies, without/with immediate reconstruction)

[Mode 4; median 4; IQR 4-5]

Similar to DCIS, the anterior margins in case of mastectomy, regardless of the type of procedure, are often not reported, unless the intent is to report skin involvement (T4b, c, d). Re-excision is not standard procedure after mastectomy despite close margins unless there is evidence of skin involvement [52]. This may relate to surgical protocols for modified radical/total mastectomies including resection of the skin overlying the tumour site, and early skin sparing mastectomy (SSM) or NSM techniques which sacrificed the skin overlying the tumour site while still adhering to a skin preserving approach [46, 52]. The skin/subcutis overlying the tumour bed were shown to contain potential residual disease, even if there was no clear evidence for residual breast glandular tissue, due to lymphovascular invasion [59]. A DCIS component was responsible for most of the positive superficial specimens overlying invasive component, implying that the nature of DCIS makes it difficult to predict the extension of disease [59]. Some surgical guidelines have a high focus on surgical complications and aesthetic outcomes rather than oncological safety and eligibility for SSM/NSM versus total mastectomy [60]. Current SSM/NSM are performed with pre-planned incision regardless of the tumour site aiming to achieve better aesthetic results and less postoperative complications, which has been related to a higher rate of involved margins due to the thickness of the skin flap [50, 52, 61, 62]. Importantly, independently of the surgical incision and removal of overlying skin, the skin-flap thickness and related complications are highly dependent on the surgeon´s expertise [63, 64]. Over 90% of all local recurrences after these procedures occur within five years suggesting subclinical residual disease and residual breast glandular tissue [52, 65, 66].

Panellists' comments: Preoperative imaging can assist in estimating the extent of disease and proximity to the skin to plan the surgical procedure. Treatment decisions, including the type of surgical procedure, and potential benefits of primary systemic therapy, and the need of PMRT should be discussed in a multidisciplinary meeting. The panel strongly advises re-excision in these cases. Use of bolus and boost are related to acute and late toxicities, including fibrosis,

[67] and are independently associated with complications in the setting of breast reconstruction, including infection, skin necrosis, implant failure and do not necessarily lead to superior local control [68]. Nevertheless, treatment decisions about re-excision, use of bolus and boost (if the area can be located) should be based on medical and oncologic disease outcomes rather than on aesthetic considerations, and the patient should be involved in the decision.

2.3 The panel *agrees* that bolus is indicated in case of skin involvement or inflammatory tumour stage (T4b, c, d or any ypT4).

(*statement for total mastectomy. NSM/SSM are not recommended for T4b, c, d)

[Mode 5; median 5; IQR 4-5 (T4b, c)]

[Mode 5; median 5; IQR 5-5 (T4d or ypT4)]

As indicated in the ESTRO target volume delineation for elective radiation therapy of early-stage breast cancer consensus guidelines [41, 42], in case of T4b, c, d tumours, the chest-wall skin is part of the clinical target volume. Therefore, bolus is indicated to achieve coverage with 95-100% of the prescribed dose.

Panellists' comments: Bolus is recommended when preoperative clinical findings of carcinoma fixed to the skin with/without skin or nipple retraction strongly suggest epidermal or dermal involvement without pathological confirmation.

2.4 The panel *agrees* that bolus is indicated only in cases where the skin is at high risk of recurrence (on a case-by-case basis).

[Mode 5; median 5; IQR 4-5]

Discussed in above and below.

Panellists' comments: Based on the data provided in this report.

2.5 The panel *agrees* that bolus should be routinely used in cases of chest-wall *recurrence.*

[Mode 4; median 4; IQR 4-5]

In case of RT for chest-wall recurrence, the subcutaneous tissue and skin should be covered by the 95-100% isodose line by using a bolus. Approximately 82% of the local recurrences are within the subcutaneous tissue and/or skin, with most of the remainder found in the pectoralis muscle. Rib, sternal and intercostal muscle recurrences are uncommon [6, 69] and considered distant recurrences [70]. Seldomly, the loco-regional recurrence (LRR) was a result of direct invasion e.g., from tumour involvement of retro-pectoral/Rotter's lymph nodes, internal mammary nodes [71].

Panellists' comments: A decision should be made to balance potential benefit and harm of bolus use in case of re-irradiation. Re-irradiation protocols and techniques are associated with, sometimes severe, toxicity, thus careful evaluation of the patient prior to re-irradiation, evaluation of dosimetric data and toxicity from previous RT, and meticulous planning including discussing the benefits of the bolus is advised [72].

2.6 The panel *agrees* that bolus should be routinely used in cases of inoperable breast cancer or fungating mass.

[Mode 5; median 5; IQR 4-5]

This scenario refers to breast cancers that did not respond or progressed after systemic therapy and surgery is unlikely to achieve complete excision of the tumour lesion with clear margins, loco-regional recurrent tumours after an initial primary breast cancer, or in the context of recurring or newly diagnosed metastatic disease. These tend to be more aggressive tumours. Dermal lymphovascular invasion may lead to satellite skin nodules, classified as T4b [46]. Therefore, the subcutaneous and skin should be covered within the 95-100% isodose line.

Panellists' comments: Several treatment protocols are used in these cases, and they differ in dose and fractionations without/with combination of systemic therapies. The protocols are

dependent on national/institutional guidelines and treatment objectives such as palliation, and/or to achieve response that will allow for complete resection for curative intent [73-76].

3 Consensus recommendations for bolus protocol, based on physics team summary.

3.1 If bolus is used, it should be placed at the time of CT-simulation.

[Mode 5; median 5; IQR 4-5]

3.2 If the bolus, placed at the time of CT-simulation, does not appropriately conform to the chest-wall contour, a 3D printed bolus or an equivalent conformal bolus should be considered.

[Mode 5; median 5; IQR 4-5]

3.3 A bolus of 3-5 mm is sufficient to provide acceptable dose to the surface (skin).

[Mode 4; median 4; IQR 4-5]

3.4 Bolus should be applied daily for the whole treatment course.

[Mode 4; median 4; IQR 4-5]

Panellists' comments: Placing the bolus at the time of CT-simulation (i.e., CT scan done for RT planning) allows for an estimation of how the bolus shapes to the body and identifies potential challenges. At the time of CT, the team can adjust the bolus and cut/shape the bolus to get the best fit to reduce the air gaps. This will reduce uncertainties by enabling accurate treatment planning, including considering air gaps, correct Hounsfield unit (HU) assignment for dose calculation and implicitly take into account any challenge in shaping the bolus to the body contour. Based on practical experience, a 3-5 mm bolus thickness will maintain enough flexibility to be able to shape and hold the bolus close to the skin to avoid air gaps and placement errors (as opposed to a thicker bolus like the 10 mm) and calculations show that it will also provide sufficient dose to the surface. Based on calculations performed to this work, in a typical tangential treatment plan the dose generally increases sharply in the first 10-15 mm below the skin and then starts drops again. Therefore, increasing bolus thickness (e.g., 10 mm

or thicker) shifts this peak dose closer to the skin, which may explain increase toxicity rates associated with thick bolus[7, 32]. Therefore, it is estimated that by using a 10 mm bolus the skin dose is probably closer to 105% of prescribed dose. An ideal bolus material should have tissue equivalence and sufficient flexibility, which can be achieved with a 3-5 mm bolus, without overdosing the skin. Accurate fitting of the bolus to the patient skin is important and thus, customized boluses with better fitting have been studied and implemented in clinical applications. These could be useful in particularly challenging anatomies, but in most cases, we find that shaping (and cutting if necessary) a standard sheet bolus to the patient surface is sufficient [77]. For accurate calculation and assuring at least 95% coverage it is recommended that bolus be used on every fraction if full dose to the skin is required. Daily bolus was found to be associated with increased skin toxicity compared to alternating days, but the consensus recommendation is to apply just 5 mm bolus and only in cases of T4b, c, d or any ypT4 or any high risk of skin involvement, thus daily bolus will allow full dose coverage to the high-risk regions. It is recommended that each RT department has clear protocols for bolus fitting and use according to on-site measurements.

4. Consensus about items that *do not* serve as a sole indicator for bolus use are available in appendix 4.

Nichol and colleagues [6] compared outcomes of mastectomy in patients without skin involvement and reported local recurrence rate of 1.9% with bolus and 0.9% without bolus. In their multivariable analysis for local recurrence, the hazard ratios for the following prognostic and predictive variables were of expected magnitude and direction of effect, although none of them were significant because of the low number of events (33 local recurrences/ 1887 patients): stage 3 versus 1 (HR = 3.1, 95% CI 0.4-23.6), grade 3 (HR = 2.7, 95% CI 0.6-12), positive margins (HR = 2.4, 95% CI 0.7-8.6), hormone therapy use (HR = 0.6, 95% CI 0.2-

2.5) and chemotherapy use (HR = 0.4, 95% CI 0.1-1.6). Bolus use was not significantly associated with the risk of local recurrences (HR = 1.4, 95% CI 0.3-6.4, p = 0.6) in the multivariable analysis. Additionally, bolus use did not reduce the risk of local recurrences among the patients treated with immediate reconstruction or among high-risk patients [6].

Panellists' comments: Multiple risk factors might be relevant for treatment decisions such as the use of PMRT and systemic therapies but are not necessarily indications for bolus use.

5. **Other considerations, including clinical items for which a consensus was not achieved and contraindications to bolus use, survey results are available in the** appendices **5-7.**

Discussion

Herein, we summarize the consensus recommendations for the use of bolus in the setting of PMRT, regardless of the mastectomy procedure and whether immediate reconstruction was performed. Oncology practice guidelines provide valuable support of everyday practice for oncologists to improve the safety for the patients. Oncology and radiation oncology practice guidelines, whether national or international, should be based on evidence with a transparent appraisal of the data they are based upon, and the process performed to achieve a consensus recommendation [33]. Therefore, all data of the consensus process are presented within the paper and the appendices.

Our group has reached a consensus that bolus increases side effects associated with PMRT and does not improve local control for patients without a high risk of skin involvement. Therefore, our recommendations are that in the PMRT setting, bolus should only be used for skin tumour involvement or inflammatory tumour stage (T4b, c, d or any ypT4), inoperable or fungating masses, involved superficial margins with DCIS or invasive breast cancer, and treatment of breast cancer local recurrences. In selected cases, customized bolus can be used to increase

radiation dose to identifiable, superficial, high-risk regions. The panel did not identify contraindications for the use of bolus (see appendix 7).

Risk factors (or their impact) for local recurrence may widely vary according to locoregional and systemic therapies. For example, risk factors for local recurrence after breast-conserving therapy differ from those after mastectomy [78]. Young age, a major predictive risk factor for local recurrence after BCT, is inconclusive as a risk factor for recurrence in case of mastectomy [79-82]. Additionally, in many studies, the reported rates and risk factors refer to locoregional recurrences, including regional recurrence-risk factors rather than only those linked to true local recurrences [78, 83]. Predictive factors for purely local recurrences after mastectomy are rarely reported [69, 83]. Early detection, systemic therapy and locoregional treatments improve disease outcome and survival. Early detection by screening programs reduces the risk of breast cancer death by a median of 15% (range 7 to 23%), which is of a similar magnitude to the percentage of the reduction attributable to adjuvant systemic therapy (median of 19%, range 12 to 21%) [84]. The presumed explanation is that early detection increases the proportion of cancers that can be treated prior to systemic spread or at a tumour burden that can be eradicated with surgical, systemic therapies and RT. Hence, more recent studies have reported lower rates of local recurrences after mastectomy with negative surgical margins ranging from 0.9 - 3% at a follow up of 5-10 years than older studies [6, 82, 83, 85, 86]. Additionally, recent studies did not demonstrate a significant impact of disease stage or biological subtype on local recurrence, probably linked to reduced statistical power because of lower recurrence rates thanks to more effective locoregional and systemic treatments [6, 82, 85, 86]. Similarly, lymphovascular invasion, which was considered a risk factor for local and regional recurrences in older studies [87], was not associated with increased risks of local recurrences after mastectomy in newer studies [6, 82, 85, 86]. Park et al. reported that lymphovascular invasion was associated with a significantly elevated risk of regional but not local recurrence [86]. An important factor that

consistently contributed to a high local recurrence rate after mastectomy was a positive surgical margin. A systematic review of literature published from 1980 to 2019, analysing 34 studies and 34,833 mastectomy patients (invasive and DCIS), reported in a subgroup analysis that after SSM, positive margins were associated with increased local recurrence rates [HR 3.40, (95%CI 1.9-6.2)]. Studies were grouped by their description of a positive margin and all descriptions of a positive margin were associated with increased local recurrences (tumour at ink: HR 2.77 (95% CI 1.70, 4.54), <1 mm: 3.15 (95% CI 1.70, 5.82), <2 mm: 2.78 (95% CI 1.41, 5.49)) [88]. This observation was supported by Yap and colleagues [9] in patients treated with PMRT. In their study, positive margins were the most important predictor of local recurrences and the risk of local recurrences with positive margins was high (14%), even when bolus was used. Thus, RT cannot salvage poor surgery and clear margins are needed to reduce the risk for local recurrences. Close or positive margins after mastectomy are associated with a two to three-fold increased risk of local recurrences in comparison to negative margins for invasive cancer regardless of PMRT was performed [88]. PMRT might reduce local recurrences in patients who underwent mastectomy for pure DCIS with involved margins [47, 54].

In our opinion, more work is needed to establish guidelines to reduce recurrences after mastectomy, which include: 1) selecting the optimal surgical procedure based on oncological safety assuring clear margins, 2) appropriate training of the breast surgical team to safely resect all tumour, areas of subcutis that are at high risk, and reduce skin flap thickness in case of SSM/NSM, 3) assessing and reporting of surgical margins (importantly, superficial margins) in light of innovative surgical techniques, 4) reducing / managing positive-close margins, 5) better understanding of postmastectomy target volumes according to factors such as disease stage, histopathologic and molecular features (e.g., lymphovascular invasion), genomic profile, to allow for adaptation of the dose distribution according to these features rather than "bolus to all" approach.

It is imperative to understand that the indications for PMRT are not the same as the indications for the use of bolus. Considering the low rates of local recurrences for patients without skin involvement treated with PMRT with or without bolus (~ 3% in 10-years) [6], and the fact that only approximately a third of these local recurrences occur in the skin [69], only 1% of the patients could hypothetically have their risk of local recurrence reduced using bolus. Generously presuming that all patients treated without bolus have local recurrences and that no patient treated with bolus has local recurrences, the number needed to treat is 100 to prevent one local recurrences at 10 years. Meanwhile, there is evidence from 13 PMRT studies that the pooled risk of grade 3 acute toxicity is 9.6% with bolus and 1.2% without bolus - a number needed to harm of 12 [1/(9.6% - 1.2%)]. It is reasonable to conclude that the use of bolus is ~ 8 (100/12) times more likely to cause documented harm than hypothetical benefit.

In summary, we cannot conclude that using bolus reduces the risk of local recurrences as there are no randomised trials that determine the efficacy of bolus, and the retrospective evidence is limited. We do know, however, from dosimetric studies, that bolus use increases the dose to the skin and, from clinical studies, that treating the skin with up to 100% of the prescribed dose increases the risk of early and late toxicity. Therefore, 3-5 mm of daily bolus full chest-wall is indicated only in rare, highly selected cases, where the skin is deemed to be within the clinical target volume. Additionally, custom bolus, to a limited area at risk can be considered to reduce unnecessary toxicity and achieve a better dose distribution to the target volume.

It is our wish that this consensus paper will be used by RT-team members to optimize the use of bolus except in cases where the benefit is likely to outweigh risk. This fulfils our mutual responsibility to provide safe and effective treatments to our patients. The breast cancer RT environment should commit themselves to validate the use of this consensus by reporting the morbidities and recurrence pattern in all patients treated according to the consensus.

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A Delphi study and International Consensus Recommendations:

The use of bolus in the setting of postmastectomy radiation therapy for early breast cancer

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Highlights

- In the setting of Postmastectomy radiation therapy (PMRT) bolus was not proven to reduces the risk of local recurrences.
- The use of bolus for PMRT increases the risk of early and late toxicity.
- The use of bolus should be limited to highly selected cases, where the skin is deemed to be within the clinical target volume.

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