

Using the Bolus in Post-mastectomy Radiation Therapy (PMRT): A National Survey on Behalf of the Italian Association of Radiotherapy and Clinical Oncology (AIRO) Breast Cancer Group

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Abstract. *Background/Aim:* This study aimed to investigate the bolus practice among Italian radiation oncologists. *Patients and Methods:* In 2018, a survey on bolus application was sent to all members of the Italian Association of Radiotherapy and Clinical Oncology. *Results:* The survey was joined by 102 radiation oncologists. Not all respondents answered to every question. A 69.5% of 82 respondents used bolus in case of skin infiltration and 52 of 68 respondents (76.5%) applied it every day. Skin was included as part of chest wall Clinical Target Volume both in the absence or the presence of breast reconstruction. Five mm bolus was the most used. 3D Conformal radiotherapy was the most used technique, in 73.5% of cases. Acute RTOG G2-G3 skin toxicity was recorded by 93.9% physicians. *Conclusion:* There was heterogeneity in the use of bolus, though an agreement was found in some topics. The achievement of a National Consensus may represent an interesting future goal.

Post-mastectomy radiation therapy (PMRT) has been demonstrated to improve locoregional control and overall

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survival for patients with high risk breast cancer recurrence in several studies. Chest wall represents the anatomical region with the highest risk of recurrence (1-7); main factors influencing the recurrence rate are: primary tumor size, nodal status, positive margins, tumor grade and lymphovascular invasion (8, 9).

Bolus is a tissue equivalent material, with atomic number and density similar to tissue or water, placed on the chest wall to spread the area that is covered by the 95% isodose increasing the surface radiation dose (10).

Up to now, its application remains controversial with some uncertainties about its routine application, especially concerning the timing (every day or less frequently). Moreover, a large variability about bolus thickness between different Radiation Oncology Departments has been reported (11).

However, the use of a bolus has been reported to increase the frequency of severe radiation dermatitis. Therefore, the advantage in terms of reduced risk of local recurrence could be thwarted by increased acute skin and subcutaneous tissue side effects that might require interruption of the radiation treatment with a potential detrimental impact on local control (12, 13).

Finally, late cutaneous/subcutaneous toxicities could occur, when breast prosthesis are present, with a potential worsening of the cosmetic result (14).

To the best of our knowledge, routine use of a bolus was mentioned only in ASCO guidelines published in 2001 with a low grade of evidence about its recommendation (15).

In this context of uncertainties, the aim of this survey was to investigate bolus routine practice among Italian radiation

Table I. *Questions of the survey (clinical topics, contouring and physical topics, treatment topics).*

Introduction topics	
1	Hospital category
2	Experience in breast cancer treatment
Clinical topics	
3	In clinical practice, when is bolus applied in PMRT setting? (Multiple choice question)
4	In case of close margins, when is bolus used? (Multiple choice question)
5	How frequent is bolus applied during radiation treatment in each patient? (Multiple choice question)
6	Is bolus application frequency conditioned by clinical presentation?
7	If yes, which clinical presentation? (Open ended question)
8	Does chest wall thickness influence the decision for bolus application?
9	Does a possible breast reconstruction influence the decision for bolus application?
10	In case of absence of breast reconstruction, which is the bolus thickness?
11	In case of breast reconstruction, which is the bolus thickness?
Contouring and physical topics	
12	In case of absence of breast reconstruction, how is chest wall CTV delineated?
13	In case of breast reconstruction, how is chest wall CTV delineated?
14	How is bolus applied in the planning treatment phase?
15	For PMRT are photons or electrons used? (Multiple choice question)
16	In case of bolus application, which is the radiotherapy technique used? (Multiple choice question)
17	In case of absence of bolus, which is the radiotherapy technique used? (Multiple choice question)
18	What is bolus made of?
Treatment topics	
19	How is bolus fixed to chest wall without breast reconstruction? (Open ended question)
20	How is bolus fixed to chest wall in case of breast reconstruction with expander/prosthesis? (Open ended question)
21	In your experience, what grade of skin toxicity, according to RTOG, is observed in case of bolus application? (Multiple choice question)

oncologists with high expertise in the treatment of breast cancer, describing its clinical, physical and technical aspects and including skin toxicity related to its application.

Patients and Methods

In November 2018, during the Italian Association of Radiotherapy and Clinical Oncology (AIRO) National Congress, the survey was proposed determining the nationwide attitude of radiation oncologists on the use of bolus regarding its application, target volume delineation, treatment planning and radiation therapy techniques in PMRT patients.

The survey was sent to all AIRO members by email without limiting the number for every Radiation Oncology Departments. Radiation oncologists were asked to answer the questions according to their own experience and daily practice; neither the names of the participants nor the total number of physicians who received the survey by email were known to the authors of this manuscript.

The survey included clinical, contouring, physical and treatment topics with 21 different questions; seven of them were multiple choice questions with the chance of giving more answers. Therefore, three were presented as open-ended questions (Table I).

The survey was hosted by SurveyMonkey (16) and answers were elaborated as results from every responder.

Results

The survey was joined by 102 radiation oncologists, although not all questions were answered.

Demographical topics

Hospital category. Forty-one (40.2%) of 102 radiation oncologists who initially joined the survey were from non-teaching hospitals, 35 (34.3%) from academic institutions and 26 (25.5%) from private care centers and cancer care centers.

Experience in breast cancer treatment. Most of participants (n=60; 58.8%) had more than 10 years of experience in breast cancer radiation treatment, 24 (23.5%) had 5-10 years of experience and 18 (17.7%) less than 5 years.

Clinical topics

In clinical practice, when is bolus applied in the PMRT setting? Most of participants (n=82) replied to this multiple-choice question. Twelve participants (14.6%) always applied bolus and 10 (12.2%) never used bolus in PMRT; fifty-seven participants (69.5%) declared to apply bolus in case of skin

Table II. *Clinical topics. A: bolus application in clinical practice. B: frequency of bolus application. C: bolus thickness according to breast reconstruction.*

A. In clinical practice, when is bolus applied? (Multiple choice question)				
Answer choices (82 respondents)	n	%		
Always	12	14.6		
Never	10	12.2		
Skin infiltration (T4 stage)	57	69.5		
Derma infiltration	17	20.7		
Positive margins	23	28.1		
Lymphovascular invasion	3	3.7		

B. How frequent is bolus applied during radiation treatment in each patient? (Multiple choice question)				
Answer choices (68 respondents)	n	%		
Always	52	76.5		
Only in the first half of radiotherapy	12	17.7		
Every other day	8	11.8		

C. Which is the bolus thickness?	Without breast reconstruction (68 respondents)		With breast reconstruction (67 respondents)	
	n	%	n	%
3 mm	3	4.4	2	3.0
5 mm	40	58.8	34	50.7
10 mm	7	10.3	6	9.0
It depends from chest wall thickness	18	26.5	25	37.3

infiltration (T4), 17 (20.7%) when derma was invaded, 23 (28.1%) in case of positive margins and 3 (3.7%) in case of lymphovascular invasion (Table II).

In case of close margins, when is bolus used? Forty-two participants answered this question with the chance of multiple answers. Bolus was applied by 61.9% of them only when superficial margin was involved, while 13 physicians (31.0%) used to apply it for every kind of positive margins (R1) and 10 (23.8%) only in the presence of not clearly identifiable margins.

How frequent is bolus applied during radiation treatment in each patient? Sixty-eight physicians answered this question with the possibility of multiple choices. Fifty-two participants (76.5%) affirmed to apply the bolus during every session of radiotherapy, 12 participants (17.7%) only in the first half of the treatment and the last 8 physicians (11.8%) every other day (Table II).

Table III. *Chest wall CTV delineation.*

Answer choices	How is chest wall CTV delineated?			
	Without breast reconstruction (69 respondents)		With breast reconstruction (69 respondents)	
	Responses (n)	Responses (%)	Responses (n)	Responses (%)
Delineation up to skin	36	52.2	35	50.7
3 mm from skin	28	40.6	29	42.1
Other	5	7.2	5	7.2

Is bolus application frequency conditioned by clinical presentation? Sixty-seven radiation oncologists answered about bolus frequency and its relationship with clinical presentation; clinical presentation did not influence bolus frequency application for most of them (56 physicians, 83.6%).

If yes, which clinical presentation? (Open-ended question) Eleven physicians (16.4%) declared that bolus frequency application was influenced by the following clinical presentation: skin invasion (5 responders), T4a/positive margins (5), derma invasion (1).

Does chest wall thickness influence the decision for bolus application? Sixty-nine radiation oncologists answered. Thirty-four (49.3%) confirmed that wall thickness influences the use of bolus, while 35 (50.7%) declared that it did not sway decision for bolus application.

Does a possible breast reconstruction influence the decision for bolus application? Sixty-nine responders answered: specifically, 39 of them (56.5%) confirmed that breast reconstruction could condition bolus application, while 30 (43.5%) were not influenced.

In case of absence of breast reconstruction, which is the bolus thickness? Sixty-eight clinicians answered. Forty responders (58.8%) affirmed that bolus thickness was 5 mm, 7 participants (10.3%) 10 mm, three (4.4%) 3 mm, whereas 18 physicians (26.5%) declared that bolus thickness depends by chest wall depth (Table II).

In case of breast reconstruction, which is the bolus thickness? Bolus thickness was 5 mm for 34 of 67 responders (50.7%), while 25 (37.3%) reported that it depended on prosthesis positioning or presence of expander; six physicians (9.0%) answered 10 mm, while 3 mm was the bolus thickness for 2 responders (3.0%) (Table II).

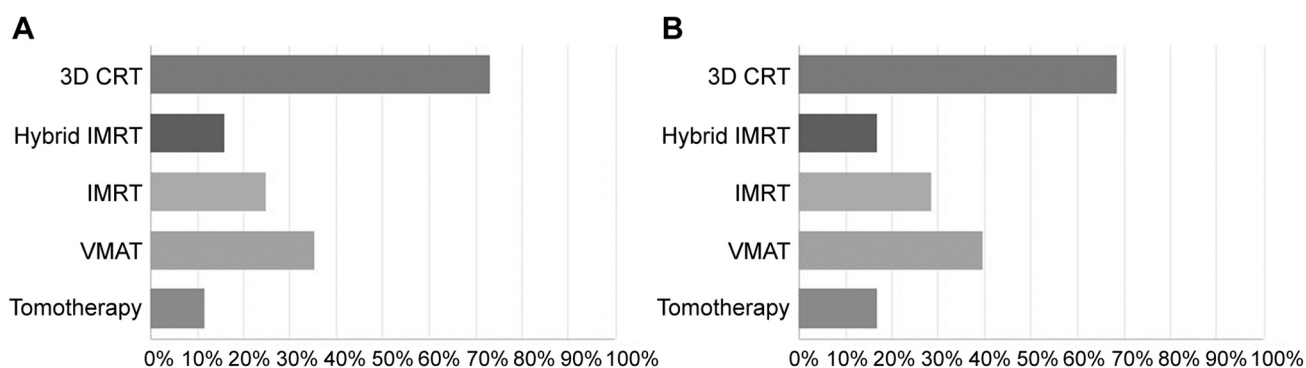


Figure 1. Radiotherapy techniques in post-mastectomy radiotherapy (PMRT). A: with bolus application. B: without bolus application. 3D-CRT: 3D-conformal radiotherapy; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy.

Contouring and physical topics

In case of absence of breast reconstruction, how is chest wall CTV delineated? Sixty-nine participants answered: 36 (52.2%) declared to delineate CTV up to the skin, while 28 radiation oncologists (40.6%) contoured CTV at a distance of 3 mm from the skin (Table III).

In case of breast reconstruction, how is chest wall CTV delineated? The responders were 69; thirty-five (50.7%) declared to delineate chest wall CTV up to the skin in case of chest wall reconstruction while it was contoured with a distance of 3 mm from the skin for 29 participants (42.1%) (Table III).

How is bolus applied in the planning treatment phase? Sixty-nine participants answered, almost equally divided between those who declared to apply bolus when simulation CT was performed (36, 52.2%) and those who delineated bolus on Treatment Planning System (33, 47.8%).

For PMRT are photons or electrons used? For this multiple-choice question, sixty-nine participants of 72 (95.8%) affirmed to use photons for PMRT, while 23 (31.9%) used electron beams.

In case of bolus application, which is the radiotherapy technique used? (Multiple choice question). Sixty-eight clinicians answered this multiple-choice question. Fifty of them (73.5%) declared that 3D conformal radiotherapy (3D-CRT) was used, 24 (35.3%) used volumetric modulated arc therapy (VMAT) technique, 17 (25.0%) used intensity modulated radiotherapy (IMRT), 11 (16.2%) affirmed to use Hybrid IMRT technique and 8 responders (11.8%) used tomotherapy.

In case of absence of bolus, which is the radiotherapy technique used? Seventy clinicians answered this question

with multiple choices: 48 (68.6%) used 3D-CRT technique, followed by VMAT technique (28 participants, 40.0%), IMRT (20, 28.6%), Hybrid IMRT (12, 17.1%) and Tomotherapy technique for 12 physicians (17.1%).

Results on radiation therapy techniques in the setting of PMRT with or without bolus are shown in Figure 1.

What is bolus made of? Sixty-six participants answered; most of them (n=59, 89.4%) declared to use a tissue equivalent gel, while 6 (9.1%) used a thermoplastic material as bolus. Only one clinician (1.5%) affirmed to use a different material.

Treatment topics

How is bolus fixed to chest wall without breast reconstruction? (Open-ended question) How is bolus fixed to chest wall in case of breast reconstruction with expander/prosthesis? (Open-ended question)

Question 19 and 20 were also open ended (regarding bolus fixation to the chest wall) and the percentages resulting from the answers are summarized in Table IV.

In your experience, what grade of skin toxicity, according to RTOG scale, is observed in case of bolus application? Sixty-six responders answered this multiple-choice question. Grade 2-3 acute skin toxicity (RTOG scale) (17) was observed by 62 respondents (93.9%) and Grade 0-1 toxicities were also by 14 physicians (21.2%). Two radiation oncologists (3.0%) noticed grade 4 skin toxicity.

Discussion

The 2005, Oxford meta-analysis showed that PMRT for node positive patients decreased significantly the chest wall recurrence risk from 21% to 7.8% and this result was also correlated with an improvement of survival (18).

Table IV. *Bolus fixation to chest wall without (A) or with (B) breast reconstruction.*

How is bolus fixed to chest wall without breast reconstruction? (Open ended question)		
Answer choices	Responses (n)	Responses (%)
Laying in contact with skin	15	26.8
Shaping to skin/Thermoplastic material	3	5.3
Adhesive materials		
Hypoallergenic patches	27	48.2
Scotch tape	8	14.3
Elastic bands	1	1.8
Film with adhesive materials	1	1.8
Ultrasound gel with patches	1	1.8
Total Respondents: 56		
How is bolus fixed to chest wall in case of breast reconstruction with expander/prosthesis? (Open ended question)		
Answer choices	Responses (n)	Responses (%)
Laying in contact with skin	11	20.0
Shaping to skin/Thermoplastic material	6	10.9
Adhesive materials		
Hypoallergenic patches	25	45.5
Scotch tape	10	18.2
Elastic bands	1	1.8
Film with adhesive materials	1	1.8
Ultrasound gel with patches	1	1.8
Total Respondents: 55		

In 2001, ASCO published PMRT guidelines with some controversies; one of the issues was the use of bolus and its frequency of application; it is used to increasing the dose on the skin when photon beams are applied (12). Our recorded data showed a heterogeneous use of bolus among radiation oncologists in Italy in terms of its indications, frequency and technical features.

In 2007, Vu *et al.* published an international survey showing that 68% of radiation oncologists used bolus in their clinical routine, with the highest incidence of bolus application occurring in the Americas (82%). Among the 26% of respondents who used a bolus for certain indications only, there was also a wide variability in the indications (skin involvement: 48%, inflammatory disease: 18%, any T4 disease: 10%, close or positive margins: 28% and positive lymphovascular invasion: 6%) (19).

As reported in current literature (7), skin infiltration was one of the high-risk factors for cutaneous recurrence.

Regardless of immediate reconstruction, from the analysis conducted by Aristei *et al.*, bolus is used only when skin is involved; however, there is no consensus for its daily use, whether to apply it on the entire wall or only on the scar as well as about its thickness. In clinical practice, most of radiation oncologists who joined our National survey applied bolus in case of skin infiltration (20).

Frequency represents a factor that could influence skin dose. Andic *et al.* have placed a 1 cm thick bolus over the chest wall for 0, 5, 10, 15, 20, or 25 treatment days in TPS calculations for all patients planned with 3D CRT. They compared the dosimetric results and concluded that using a 1 cm bolus in up to 15 of the total 25 fractions increased minimum skin doses with a tolerable increase in maximum doses (10).

The Italian trend seemed to be different in terms of frequency. Most of Italian radiation oncologists (56% of 68 respondents) declared that frequency of bolus application was not usually conditioned by clinical presentation (e.g. skin infiltration, positive margins, derma infiltration, skin toxicity during radiotherapy). Our results showed that the highest percentage (76.5%) of physicians always applied bolus to each patient during PMRT compared to those who applied bolus during the first half of radiation treatment (17.7%) and every other day (11.8%).

In a review from Poortmans *et al.*, skin was defined as not a part of the target volume, with the exception of skin infiltration in locally advanced breast cancer (tumor stage T4b-T4d) (21); on the other hand, the AIRO guidelines suggested to include skin and muscles in the chest wall CTV with the exclusion of ribs in case of post-mastectomy without a clear margin prompting for the use of bolus application in a context of PMRT with or without breast reconstruction (22).

The ESTRO consensus also provided guidelines for CTV delineation in case of PMRT, confirming the inclusion of skin and muscles as parts of chest wall CTV (23). In the setting of post-mastectomy radiation therapy after implant-based immediate reconstruction, Kaidar-Person *et al.* have stated that the ventral or superficial part of the CTV includes the space between the skin and the superficial sides of the pectoral muscles and the implant when/where not covered by muscle (24). The dorsal or deep part of the CTV is the virtual space between the dorsal side of the implant and the pectoral muscles or ribs and intercostal muscles where no muscle is present. Whilst the ventral part is always part of the CTV, the dorsal part is only included depending on anatomical and tumor-related risk factor, such as locally advanced breast cancer with non-pathological complete response to primary systemic therapy or invasion of the major pectoral muscle and/or the chest wall (24).

Italian radiation oncologists' trend about chest wall CTV delineation, emerged from our survey, was in line with the main literature and guidelines.

Regardless clinical presentation and presence of high-risk factors, consistent percentages of physicians included skin as a part of chest wall CTV both in case of absence and in case of presence of breast reconstruction (52.2% of 69 respondents and 50.7% of 69 respondents).

Bolus thickness presented also heterogeneity in the daily practice of clinicians; although Das *et al.* in 2017 (25) prospectively followed patients who underwent PMRT treated with 2 mm of daily chest wall bolus and found no local recurrences and low grade skin toxicity, our results showed highest percentages of respondents who applied a 5 mm bolus for PMRT patients (58.8% and 50.7%, without and with breast reconstruction, respectively).

The findings of our work were comparable with the results of one survey conducted in California and published in 2015 by Mayadev *et al.* that recorded a percentage of 80% of physicians who used a 5 mm bolus (26).

Also, in Italy, 5 mm-bolus was found as the most common choice regardless of breast reconstruction. About the radiotherapy technique, no evidence in current scientific reports was found with the aim of significantly reducing complication rates related to radiation treatment (22); this survey reported an extensive use of 3D CRT among Italian radiation oncologists in case of bolus application (73.5% of clinicians).

In the study conducted by Yap *et al.*, bolus was applied in 52 of 314 patients and both acute skin toxicity and local recurrence rates were analyzed with a median follow-up of 4.2 years. The use of bolus was reserved for patients who were considered at high risk of local recurrence, including those with dermal lymphatic invasion and positive margins. Bolus frequency was either daily or alternate daily. Local recurrence rate was 14% in the patients treated with bolus and 3.5% in the group of patients without bolus; this result was also correlated with high-risk factors in the subgroup of patients with bolus, such as T4 stage and positive margins.

Furthermore, authors found a significant difference in acute skin toxicity between the bolus and non-bolus group. The bolus group had a higher rate of grade 2 skin toxicity equal to 40% versus 21% in the non-bolus group (7).

Results from our survey demonstrated a high prevalence of acute G2-G3 skin toxicity based on RTOG scale (93.9% of 66 respondents) when bolus was used.

Finally, a limitation of this work was the relatively small number of responders but, compared to other international Surveys, the results seemed to be enough to understand the general trend for use of bolus in PMRT in the different Italian institutions.

In conclusion, although our data confirm the large heterogeneity in the clinical practice, some of our results are in line with the literature. Skin infiltration (69.5%) and positivity of margins, especially when superficial margin was involved (61.9%), remained the most influencing factors for

the use of bolus. Standard 3D-CRT was the most used technique in PMRT though the increase in special radiotherapy techniques could compensate bolus application. Future prospects and objectives could be the achievement of a National Consensus, starting from the topics with more agreement in our survey.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

MN, LAU and DG designed and coordinate the study and the analysis. MN, LAU and FP collected the data. CR, MDT, MT, IM, FG, AC and LC reviewed and approved data selection. FP, CR and MDT performed main data analysis and provided pictures elaboration. MN, LAU, FP, CR and MDT drafted the article. MT, IM, FG, AC, DG and LC critically revised the study and the article. All Authors reviewed and approved the final article.

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