The Assisi Think Tank Meeting Survey of post-mastectomy radiation therapy in ductal carcinoma in situ: Suggestions for routine practice

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Abstract

Background: Risk factors for local recurrence after mastectomy in ductal carcinoma in situ (DCIS) emerged as a grey area during the second "Assisi Think Tank Meeting" (ATTM) on Breast Cancer.

Aim: To review practice patterns of post-mastectomy radiation therapy (PMRT) in DCIS, identify risk factors for recurrence and select suitable candidates for PMRT.

Methods: A questionnaire concerning DCIS management, focusing on PMRT, was distributed online via SurveyMonkey. .

Results: 142 responses were received from 15 countries. The majority worked in academic institutions, had 5-20 years work-experience and irradiated <5 DCIS patients/year. PMRT was more given if: surgical margins <1mm, high-grade, multicentricity, young age, tumour size >5 cm, skin- or nipple- sparing mastectomy. Moderate hypofractionation was the most common schedule, except after immediate breast reconstruction (57% conventional fractionation).

Conclusions: The present survey highlighted risk factors for PMRT administration, which should be further evaluated.

Keywords: Breast cancer, Ductal carcinoma in situ, Post-mastectomy radiotherapy, Hypofractionation, Survey

1. Introduction

Until the introduction of breast cancer population screening programs, diagnosis of ductal carcinoma in situ (DCIS) was infrequent, being found in less than 5% of all new cancer diagnoses. At present, DCIS accounts for 20-25% of all new cases [1].

After breast conservative surgery (BCS) for DCIS, whole breast radiation therapy (WBRT) demonstrated its efficacy and safety by significantly reducing both in situ and infiltrating local relapses. Four large randomized studies with more than 12 years' median follow-up as well as meta-analyses of these studies, including one by the Early Breast Cancer Trial Collaborative Group, confirmed the benefit of WBRT in all patients, independently of age, size, grade, surgical margin status or presence of comedonecrosis [2-9]. WBRT may however, be omitted for women with very low risk tumours who, after discussing the pros and cons with their physicians, accept a small but significant increased ipsilateral relapse rate.

Since DCIS is considered a precursor of a potentially infiltrating malignancy, total mastectomy should constitute sufficient treatment and in fact, local recurrence rates are generally low. Mastectomy rates for DCIS have been rising again over the last few years and it has become the selected surgical option for almost 30% patients [10,11] particularly for women in the youngest age-group and those with high-risk factors for relapse after BCS and WBRT e.g. multicentricity, large and/or high grade tumours, involved resection margins.

PMRT in pure DCIS is not routinely recommended as its role has not yet been well defined. For patients harbouring "high risk" factors several recent studies evaluated post-mastectomy RT (PMRT) [12-19]. Consequently, identifying risk factors for recurrence after mastectomy is currently one of the main challenges in optimal DCIS management. Other controversial issues are whether to prescribe adjuvant endocrine therapy, and which drugs to use (tamoxifen or aromatase inhibitors).

One of the topics during the second "Assisi Think Tank Meeting" (ATTM) on Breast Cancer [20](1st-3rd March 2018), which was endorsed by the European Society for Radiotherapy & Oncology (ESTRO), was the therapeutic approach in DCIS. A grey area that emerged during the discussion was the need to identify risk factors for local recurrence after mastectomy so as to select suitable candidates for PMRT. A questionnaire was designed to review the practice patterns of PMRT in the setting of pure DCIS and consensus was reached on key clinical questions that needed investigation in future

clinical trials. The results of the survey and key points for the ATTM discussion of PMRT in DCIS are presented below.

2. Material and methods

The DCIS group at the ATTM designed a questionnaire based on current scientific literature, which was reviewed by the Expert Board Members (radiation and clinical oncologists who were experts in breast cancer) and subsequently revised in accordance with their comments. The questions raised in the questionnaire arose from the discussion held at the ATTM group meeting in March 2018. After an in-depth review of DCIS topic, its treatment options and the role of modern radiotherapy in its management, the greatest discrepancies were observed respecting to the role of PMRT after DCIS. As a result, the possibility was raised of gathering the opinion of a greater number of experts in breast cancer radiotherapy to obtain a real image of the role of PMRT in the context of the multidisciplinary treatment of DCIS. Questions raised are intended to explore existing gray areas regarding DCIS post-mastectomy radiation: when, how and why. Between June and July 2018, the questionnaire was distributed online to each ATTM participant via the online survey cloud-based software "SurveyMonkey" (SurveyMOnkey Europe, UC, Dublin, Ireland). Each participant was requested to answer the questionnaire and forward it, directly or via scientific societies, to colleagues who were active in the field of breast cancer. We suggested that per department only one reply was given, by the reference person for breast cancer. Items in the questionnaire referred to diverse aspects of DCIS management but focused on PMRT indications. The first 3 questions (Q1, Q2, Q3), addressed general topics such as country, institution type and years of experience in RT for breast cancer. Five questions referred to institutional experience with PMRT in DCIS and related risk factors (Q4, Q5, Q6, Q7, Q8). Three questions inquired about the influence of the different types of mastectomy and reconstruction on indications to PMRT (Q9, Q10, Q11) and seven (Q12, Q13, Q14, Q15, Q16, Q17, Q18) focused on technical aspects of RT. Three more questions (Q19, Q20, Q21) investigated bio-pathological DCIS characterization and addressed the issue of endocrine treatment. The last two questions (Q22, Q23) asked whether respondents were willing to participate in both retrospective and prospective studies, should the opportunity arise in the future.

Survey participation was voluntary with no financial incentives. Ethical Approval was non-required.
Data are presented by descriptive statistics.

3. **Results**

A total of 142 participants from 15 countries answered the 23 survey questions (Q1) (Fig 1). The majority of responders (76.8%) were from academic institutions while 19.7% worked in General Hospitals (Q2). The expertise of responding radiation/clinical oncologists (from now on referred to as radiation oncologists) ranged from under 5 years for 4.9% to over 20 years for 50% (Q3) (Table 1). Mastectomy for DCIS was limited to under 50 patients/year in most institutions but >100 patients/year received it in nearly 8% (Q4). The main factors for PMRT were close (<1mm) surgical margins (80.6%), high grade (37.5%) and multicentricity (28.5%). The strength of the indication increased with additional risk factors, including young age and tumour size >5 cm (Q7, Q8) (Table 2).
With or without immediate breast reconstruction (IBR), PMRT was rarely or never indicated by 90% of respondents and 85.9% declared they delivered it to under 5 patients a year (Q5, Q6). Whether IBR was autologous or heterologous (Q9, Q10) did not change the recommendation for PMRT for more than half of responders. To note 16.9% of radiation oncologists considered skin-sparing or nipple-sparing mastectomy as a major factor for prescribing PMRT (Q11) (Table3).
In cases of PMRT, 50% of radiation oncologists recommended a radiation boost on the surgical scar only when margins were close or positive, whether with IBR or not (Q12). Complex advanced RT techniques (intensity modulated RT, volumetric arc therapy, tomotherapy) were not preferred by 65% of radiation oncologists and were reserved, for the most part, for situations that could not be adequately treated with conventional techniques, including field-in-field "forward-planned IMRT" (Q13). Nearly two-thirds (64%) of radiation oncologists recommended using a bolus on the chest wall during treatment (Q14) (Table 4).
Moderate hypofractionation (2.5-3 Gy per fraction) and a conventional scheme (2 Gy per fraction) were used for PMRT (44.36% and 40.84%, respectively). In the presence of IBR, more than half of radiation oncologists (57%) chose a conventional scheme. Likewise,

when a boost was needed, most responders favoured a conventional scheme of 2 Gy/day for the whole treatment, independently of IBR (Q15, Q16, Q17, Q18) (Table 4).

Immunohistochemistry was routinely performed in most institutions for quantitative determination of oestrogen receptor (78.9%), progesterone receptor (71.1%) as well as Ki-67 (54.9%) (Q19). In the presence of positive oestrogen receptors endocrine treatment was prescribed depending upon age, grade, margins or tumour size, by 69.6% of radiation oncologists, 47% of whom recommended tamoxifen (Q20, Q21) (Table 5).

Finally, survey responders were asked whether they were willing to participate in retrospective or prospective, observational or randomized trials on the use of PMRT in DCIS. More than 86% agreed to do so (Q22, Q23) (Table 6).

4. **Discussion**

The present survey investigated how radiation oncologists from different countries manage PMRT in DCIS. Although mastectomy is used in about 30% of patients, PMRT is rarely administered because local recurrence rates range from 0% to 7.5% [21], and 15-year breast-cancer related mortality rates from 1.74% to 2.26%. The latter is almost the same after mastectomy or BCS, whether patients received radiation therapy or not [22]. Local recurrences after mastectomy are, however, mostly invasive and are associated with 10-15% long-term metastases risks and poorer overall survival [12,13,21,24,25]. Using the University of Southern California/Van Nuys Prognostic Index, Kelley et al. analysed data from 496 patients treated with mastectomy, none of whom received any form of adjuvant treatment. The 12-year probability of disease recurrence was 9.6% for patients scoring 10-12 *vs* 0% for those scoring 4-9 ($p = 0.0004$). The authors concluded that 10 of every 100 patients with USC/VNPI scores of 10-12, will relapse within 12 years and 2-3 will develop metastatic disease [15].

Although the role of WBRT in reducing in situ and invasive local failure rates even in women with low-risk tumours has long been established [8,26,27], clear indications for PMRT have yet to be defined. Since few retrospective studies, often with small cohorts, have investigated the topic, identifying appropriate risk factors seems crucial to justify PMRT in patients with DCIS [13-19,25], and even more, when the number of mastectomies for the treatment of DCIS is increasing in recent years, including an increasing tendency to perform a bilateral mastectomy at the diagnosis of DCIS [28].

Margin status plays a major role in local recurrence. Almost one-fifth of UK breast surgeons would consider PMRT in pure DCIS with close/positive margins [23]. Rashtian et al. observed that mastectomized patients with high-grade DCIS and resection margins <2 mm presented local recurrence rates of 16% *vs* 2% when the margin was >2 mm (p = 0.035) (13). Likewise, Childs et al. observed, at a median follow-up of 7.6 years, 4.5% local recurrence rates in 44/142 patients with DCIS after mastectomy when margins were positive or close [16]. Despite higher local recurrence rates in other series of mastectomized patients with pure DCIS and close/positive margins, the rates of chest wall recurrences were so low that no firm recommendation could be provided for or against PMRT [14,17-19]. In a review of data from more than 21,000 DCIS patients who underwent mastectomy and were included in the National Cancer Database, Jones et al showed, however, that PMRT in DCIS was significantly more frequent with close/positive (16%) margins than with negative margins (1.5%) [29].

Additional unfavourable features supporting the administering of PMRT are high-grade disease, comedonecrosis, and age< 50 or 60 years [13,17]. Bannani et al. analyzed post-mastectomy loco-regional recurrence rates in 218 women who underwent mastectomy for DCIS or DCIS with microinvasion. After a mean follow-up of 3.2 years, 8 women (3.67%) developed local recurrences, and 2/8 had simultaneous distant metastasis. In this series, only age <40 years at initial diagnosis was identified as a risk factor for loco-regional relapse, as none of the other factors emerged as significant [25]. The present survey confirmed that for 80.6% of responders, margin status (close <1mm) played a major role in decision-making for PMRT even though most radiation oncologists also considered other risk factors, mainly, high grade, multi-centricity, young age and tumour size over 5 cm.

Surgical approaches also appear to play a role in local recurrences. Skin-sparing mastectomy (SSM) was associated with more local recurrences than standard mastectomy [30.31]. A retrospective analysis by Carlson et al. including 223 women with DCIS treated by SSM revealed a 5.1% loco-regional recurrence rate. In SSM, close surgical margins <1 mm and high-grade disease emerged as risk factors for local recurrence [30]. Timbrell et al. observed a higher rate of loco-regional recurrence after SSM versus simple mastectomy (5.9% *vs* 0%, p = 0.012). Again, the presence of close or involved margins was, along with young age, the main risk factor for loco-regional recurrence [31]. In the present survey, skin -sparing or nipple-sparing mastectomy were considered major factors supporting PMRT for 16.9% of radiation oncologists.

Another issue is the PMRT schedule in DCIS. Moderately hypofractionated RT schemes are now standard in adjuvant treatment of invasive breast carcinoma [32-36], and in DCIS several studies observed no differences comparing moderate hypofractionation with traditional 5-week schemes [37-42]. Whether a boost was required to the surgical scar or not, of all the proposed RT schedules moderate hypofractionation (2.5-3 Gy per fraction) was most popular among responders.

Increasingly, patients undergoing mastectomy are demanding breast reconstruction. When PMRT is necessary, questions arise regarding the type of adequate reconstruction as well as optimal sequence of surgical and radiotherapy treatments. Steadily more, using temporary tissue expanders (TTE) with later change to permanent implants or autologous reconstruction is preferred when considering PMRT [43]. This circumstance forces to increase the care that should be taken in the radiation planning process and raises, sometimes, discrepancies about the use of hypofractionated radiotherapy schemes. Despite the wide acceptance of hypofractionated schemes in PMRT, in presence of IBR the majority opted for the conventional 2 Gy per fraction.

Finally, immunohistochemical analyses were routinely performed in most institutions, even though the results did not impact on therapeutic choices. In fact present responders expressed no consensus on endocrine therapy: 42.9% would always recommend it in the presence of positive oestrogen receptors, while 33.8% would never do so and 26.6% would consider other factors (young age, comedonecrosis, high grade, etc.). Two studies demonstrated tamoxifen reduced the risk of local recurrence [44,445]; a systematic review confirmed that it reduced the risk of DCIS-related events in both the ipsilateral and contralateral breasts but had no effect on mortality rates. The number needed to treat to observe a protective effect of tamoxifen against all breast events was 15 when the medication was maintained for 5 years [46]. Two randomized studies (NSABP B-35 and IBIS-II DCIS) demonstrated that anastrazole may be an alternative in post-menopausal women with hormone-receptor positive DCIS [47,48]. Since endocrine treatment with tamoxifen or aromatase inhibitors is not free of side effects, which may discourage their use, lack of compliance among women with DCIS is a well-established problem. Adherence is reported to drop from 67% in the first year to 30% in the fifth year [49,50]. Finally, administering adjuvant endocrine therapy to all patients with hormone-receptor positive DCIS is, at least, questionable, as it is associated with a significant adverse impact on quality of life [51]. Indeed, the Danish and the Dutch breast cancer guidelines

advise not administering endocrine therapy, so oestrogen receptor status is even not assessed [52].

5. Conclusions

The results of this survey report current clinical practice on PMRT in patients with DCIS and attempts to identify patients at risk of relapse who are suitable candidates for it.

Although PMRT is not routinely used for most women with DCIS, several identified risk factors for recurrence should be discussed with patients during the shared decision-making process: positive or very close margins, high-grade tumours, multicentricity, young age, large tumour size and skin-sparing or nipple-sparing mastectomy.

According to the results of this multi-institutional international survey, radiation oncologists are very interested in taking part in future trials addressing this issue, both in retrospective analysis of accumulated experiences and in the development of prospective trials to study the efficacy of PMRT in selected cases of DCIS.

Acknowledgements. The authors thank all the other ATTM Expert Board members: Ciabattoni A, Franco P, Kouloulias V, Lancellotta V, Masiello V, Pasinetti N, Pfeffer R, Perrucci E, Pirtoli L, Selek U, Trigo L.

Conflict of interest

The authors have declared no conflict of interest

Founding

We received no financial support related to this study

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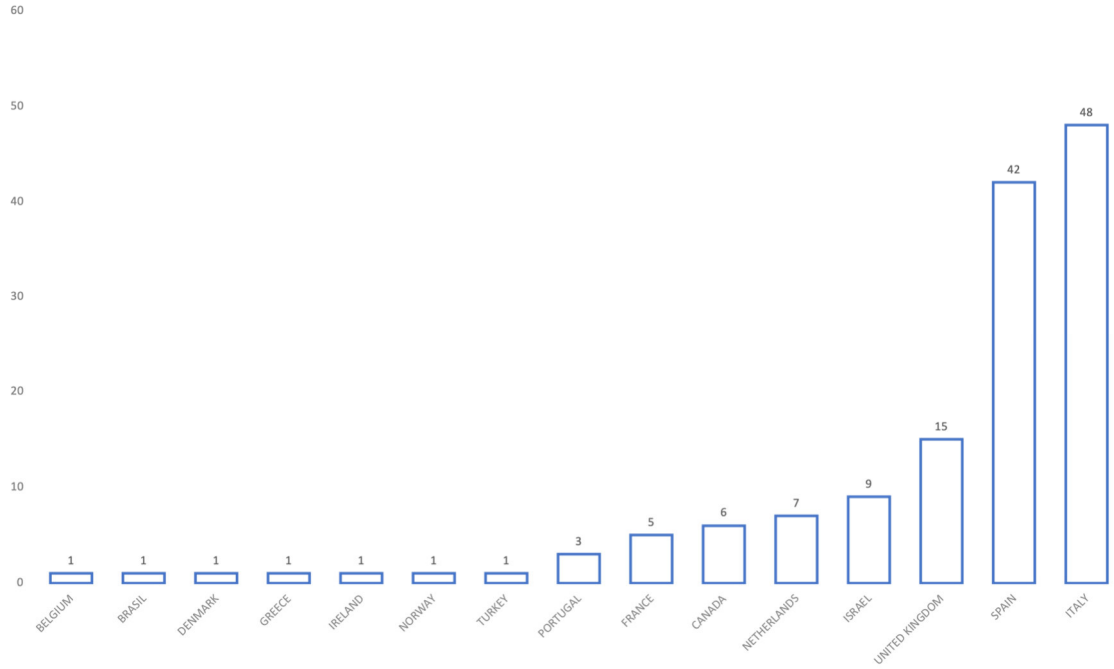
Fig. 1: number and origin of the radiation oncologists participating in the survey



Q2. What type of institution/hospital/department do you work in?	**Responders (number)**	**Responders (%)**
University institution/hospital/department	109	76.76%
Community institution/hospital/department, not university affiliated	28	19.71%
Other	5	3.5%
Q3. How many years have you been practising as a radiation oncologist?	**Responders (number)**	**Responders (%)**
<5 years	7	4.9%
5–10 years	27	19%
11–20 years	37	26.05%
>20 years	71	50%

Table 1: Survey responders' workplaces and experience (Q1, Q2)

Table 2: Clinical decision-making regarding to PMRT, according to survey responders. (Q4-Q8)

Q4. How many DCIS patients are treated per year by mastectomy in your institution during the last 5 years (please, provide the proper number of patients from your institution database) ?	**Responders (number)**	**Responders (%)**
<50 patients/year	104	73.23%
50-100 patients/year	27	19.01%
101-250 patients/year	8	5.63%
>250 patients/year	3	2.11%
Q5. In DCIS patients treated with mastectomy + immediate breast reconstruction (IBR), is postmastectomy radiation therapy (PMRT) indicated in any case in your institution?	**Responders (number)**	**Responders (%)**
Yes, in most cases	0	0.00%
Sometimes	14	9.85%
Rarely	102	71.83%
Never, patients with DCIS treated with mastectomy never received radiation therapy	26	18.30%
Q6. If yes, how many patients per year underwent PMRT during the last 5 years (please, provide the proper number of patients from your institution database)	**Responders (number)**	**Responders (%)**
<5 patients/year	122	85.91%
5-10 patients/year	15	10.05%
>10 patients/year	5	3.52%
Q7. When considering PMRT due to tumour size (DCIS >5 cm.), do you consider any other risk factors supporting PMRT indication? (multiple choice)	**Responders (number)**	**Responders (%)**
Only size >5cm	16	11.11%
High tumour grade	54	37.50%
Surgical margin <1mm	116	80.56%
Multicentriciity	41	28.47%
Simultaneous presence of extensive Lobular Carcinoma In Situ (LCIS)	10	6.94%
Other* *(Other included factors such as young age, high Ki-67, extensive comedonecrosis, as well as those not considering PMRT)	33	22.92%
Q8. When considering PMRT due to surgical margins (< 1mm.), do you consider any other risk factors supporting PMRT indication? (multiple choice)	**Responders (number)**	**Responders (%)**
Only margin <1mm	55	38.73%

High tumour grade	68	47.88%
Tumour size >5cm	53	37.32%
Age <40 years	66	46.47%

Table 3: Clinical decision-making regarding to type of mastectomy and breast reconstruction, according to survey responders. (Q9-Q11)

Q9. If the patient has been treated with IBR, do you change the indication of PMRT?	**Responders (number)**	**Responders (%)**
Always, in that case I would never indicate PMRT	9	6.33%
Never, IBR does not modify PMRT indication	81	57.04%
Sometimes	52	36.62%
Q10. If the patient has been treated with IBR, would surgical technique (heterologous vs. autologous reconstruction) change your PMRT indication?	**Responders (number)**	**Responders (%)**
Always, in cases of IBR using heterologous (prosthesis), I never indicate PMRT	3	2.11%
Always, in cases of IBR using autologous, I never indicate PMRT	4	2.81”
Never, IBR surgical modalities do not modify PMRT indication	97	68.30%
Sometimes	38	26.76%
Q11. If the patient has been treated with skin sparing or nipple sparing mastectomy, does it modify your PMRT indications?	**Responders (number)**	**Responders (%)**
Always, in cases of skin sparing or nipple sparing mastectomy, PMRT is more indicated	24	16.90%
Never, skin sparing or nipple sparing mastectomy does not modify PMRT indication	62	43.66%
Sometimes	56	39.43%

Table 4: Clinical decision-making regarding to radiation therapy techniques, according to survey responders. (Q12-Q19)

Q12In the case of PMRT following mastectomy and IBR, will you consider the use of a boost?	**Responders (number)**	**Responders (%)**
Yes, all patients are planned for scar boost (and other high risk regions)	3	2.11%
Yes, only if tumour size > 5 cm	0	0%

Yes, only in closed and/or in positive margins	71	50%
No, never	68	47.88%
Q13In case of using PMRT after IBR, is intensity modulated radiation therapy performed (IMRT, including VMAT, Tomotherapy, etc)? (not consider "forward IMRT" or "multisegments" technique)?	**Responders (number)**	**Responders (%)**
Always	22	15.49%
Sometimes	27	19.01%
Rarely – only for complex volumes or that 3D plan does not meet dose constrains	67	47.18%
IMRT is never indicated and/or is not available for these indications in my institution	26	18.03%
Q14When considering PMRT without IBR, will you use a bolus on chest wall?	**Responders (number)**	**Responders (%)**
Never	51	35.91%
Yes, daily through all the treatment	9	6.33%
Yes, on alternate days	7	4.92%
Yes, only the first half of treatment (eg. first 12-13 out of 25 fractions)	9	6.33%
Yes, depending on the treatment plan	66	46.47%
Q15What is the dose regimen used for exclusive chest wall irradiation?	**Responders (number)**	**Responders (%)**
Conventional fractionation (1.8–2.1Gy per fraction, over 25–28 fractions)	58	40.84%
Hypofractionated schedule (2.5–3.0 Gy per fraction / over 13–16 fractions)	63	44.36%
Accelerated, b.i.d. fractionation at 1.5 Gy per fraction to a dose of > 45 Gy	0	0%
Two of the above fractionations schemes, varies between cases	16	11.42%
All of the above fractionations schemes, varies between cases	2	1.40%
Other (please specify)* Other*: including never considered treatment	3	2.11%
Q16What is the dose regimen used for exclusive chest wall irradiation in case of IBR?	**Responders (number)**	**Responders (%)**
Conventional fractionation (1.8–2.1Gy per fraction, over 25–28 fractions)	81	57.04%
Hypofractionated schedule (2.5–3.0 Gy per fraction / over 13–16 fractions)	44	30.98%
Accelerated, b.i.d. fractionation at 1.5 Gy per fraction to a dose of > 45 Gy	0	0%

Two of the above fractionations schemes, varies between cases	14	9.85%
All of the above fractionations schemes, varies between cases	0	0%
Other (please specify)* Other*: including never considered treatment	3	2.11%
Q17If a boost is added to chest wall irradiation, what is your favourite schedule?	**Responders (number)**	**Responders (%)**
Conventional fractionation (1.8–2.1Gy per fraction)	70	42.29%
Hypofractionated schedule (2.5–3.0 Gy per fraction)	58	40.84%
Accelerated, b.i.d. fractionation at 1.5 Gy per fraction	0	0%
Other (please specify)* Other*: including simultaneous integrated boost or never considered boost	14	9.85%
Q18If a boost is added to chest wall irradiation after IBR, what is your favourite schedule?	**Responders (number)**	**Responders (%)**
Conventional fractionation (1.8–2.1Gy per fraction)	84	59.15%
Hypofractionated schedule (2.5–3.0 Gy per fraction)	44	30.98%
Accelerated, b.i.d. fractionation at 1.5 Gy per fraction	0	0%
Other (please specify)* Other*: including simultaneous integrated boost or never considered boost	14	40.84%

Table 5: Clinical decision-making regarding to hormonotherapy use in DCIS, according to survey responders. (Q19-Q21)

Q19. In DCIS treated by mastectomy, are there any immunohistochemistry (IHC) analysis routinely performed at your institution? If yes, what kind of IHC analysis? (multiple choice)	**Responders (number)**	**Responders (%)**
Oestrogen receptors (ER)	112	78.87%
Progesterone receptors (PR)	101	71.12%
HER2	50	35.21
Ki-67	78	54.92%
Never performed IHC analysis for DCIS	30	21.12%
Q20. In ER+ DCIS treated by mastectomy, do you consider hormonal treatment? (multiple choice)	**Responders (number)**	**Responders (%)**
Yes, always	61	42.95%
No, never	48	33.80%
Sometimes (please, specify)* Sometimes*: considered at young age, high grade, tumour size, positive margins, patient's decision,	35	26.64%
Q21. In case you consider hormonal treatment for DCIS after mastectomy, which do you choose? (multiple choice)	**Responders (number)**	**Responders (%)**
Tamoxifen	67	47.18%
Aromatase inhibitors	11	7.74%
Depending upon patient hormonal status	71	50%

Table 6: Interest in future trials participation, according to survey responders. (Q23, Q24)

Q22. In case you treat DCIS by PMRT, would you agree to participate in a retrospective study reviewing these patients?	**Responders (number)**	**Responders (%)**
Yes	123	86.61%
No	19	13.38%
Q23. If PMRT is considered for selected DCIS patients, would you accept to participate in a future randomized study?	**Responders (number)**	**Responders (%)**
Yes	124	87.32%
No	18	12.67%