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Short Communication

An additional peril of pathologic complete response

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ABSTRACT

Pathological complete response (pCR) has been shown to predict long-term outcomes in breast cancer patients undergoing primary systemic therapy in aggressive early breast cancer. Herein we discuss the caveats of determining pCR, and data needed to tailor breast cancer radiation after pCR.

Short communication

Pathological complete response (pCR) has been shown to predict long-term outcomes in breast cancer patients undergoing primary systemic therapy (PST) in aggressive early breast cancer. Therefore, pCR is considered a potential surrogate marker for improved prognosis [1,2]. However, not all trials have demonstrated survival benefits associated with pCR [3], and its prognostic value has been shown to vary by breast cancer molecular subtype, though not with residual ductal carcinoma in situ (DCIS) [2,4].

Rose and colleagues [5], in their correspondence letter argued that there is in fact *limited* evidence that trial-level pCR rate may be an effective surrogate for survival, possibly because pCR reflects the effect of therapy only on the primary tumour.

Herein, we present a short communication of a case that challenges the assumption that achieving pCR equates to locoregional disease eradication, demonstrating that recurrence can still occur despite appropriate or even "intensified" radiation therapy (due to a tumour bed boost) (Fig. 1). It should be noted that the higher rates of local recurrence rates in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2018 publication for the group undergoing PST were attributed to de-escalation of surgery and little is known on the extent of radiation in these trials [6].

In this short communication, we emphasise the pathologist's point of view of pCR after PST and how it may challenge subsequent radiation therapy.

Of special considerations is that a "pathologist-reported pCR" – is highly dependent on meticulous grossing and sampling, "the more you examine, the more you find". There is currently no global consensus for the histopathological evaluation of treatment response and more than 15 systems has been described. Some of these systems as e.g. the Miller Payne system evaluate *only* the change in the tumour at the primary site (and not the lymph nodes) and report *only* the change in cellularity of the tumour [7], whereas others, like the Residual Cancer Burden (RCB) [8], evaluate the dimensions of the tumour as well as the cellularity within the tumour after treatment and reports pCR only if *both* breast and lymph nodes are tumour free. As a consequence of varying evaluation systems being used and variation in local and individual approaches for macroscopical examination of surgical specimens after PST, the extent of sampling of tissue for microscopy may vary.

In cases of clinical complete response and/or cases with no macroscopically visible residual tumour, the entire tumour bed should be processed and embedded for microscopical examination regardless of treatment response evaluation used. In these cases, the pathology examination and report should confirm the presence of the pre-therapy marker (taking into account that clips can migrate), the biopsy tract,

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including other treatment-related changes such as destruction of the normal architecture of the mammary tissue and replacement with fibrosis or vascularised hyalinisation with presence of foamy macrophages, multinucleated giant cells, and necrosis [9]. The confirmation of these characteristics secures that the correct tissue corresponding to the previous tumour bed has been examined for residual tumour cells. Addition of immunohistochemical staining may further be applied to rule out the presence of scattered tumour cells. However, even with extensive sampling and confirmation of treatment response, there remains a possibility of under sampling of the tumour bed, with tumour cells in the sampled tissue not detected or misinterpreted as histiocytes, or tumour cells surviving therapy persisting within the residual breast tissue in the patient. Some guidelines recommend only removal of 1 cm around the clip in cases of clinically complete response [10]. Especially for luminal cancers with a poor correlation between imaging and histopathological findings after PST and a tendency for a more patchy regression of the tumour [11,12,13], this can be suspected to increase the risk of leaving tumour cells behind in the residual breast. Triple negative cancers and HER2 positive cancers are in general described to shrink in a more concentric way.

In this case, the gross specimen was of the same size as the tumour prior to therapy, and the centre of the lesion being marked was confirmed to being removed. The histopathology report indicated features consistent with a pCR. However, the occurrence of early recurrence clearly suggests the presence of residual disease resistant to therapy, including radiation therapy. This case illustrates the potential for resistant residual disease despite a pathologist-determined pCR. It underscores the need for specialised post-PST histopathological evaluation, including comprehensive macroscopic assessment and adequate sampling for microscopic review [9]. Additionally, the patient received a tumour bed boost as part of postoperative whole breast radiation therapy following pCR. A tumour bed boost is indicated in those who are at high risk of local recurrence, but it remains unclear whether a tumour bed boost provides clinical benefit after pCR, given that it increases the risk of radiation-related side effects, and that the boost target volume has been shown to contain no viable tumour cells [14,15]. Furthermore, it was shown there exists a dose-volume effect for breast induration after breast irradiation [16]. If a boost is applied, it should be small and highly targeted similar to the IMPORT-HIGH trial [17].

Using this clinical case as an example, we recommend that centres critically review their own outcomes before broadly implementing de-escalation strategies for breast and/or lymph nodes in patients achieving pCR [18]. We support prospective cohorts like the RAPCHEM (BOOG 2010–03) registry as a mean to optimize treatment, especially as it includes an analysis according to compliance with the radiation guidelines [19]. While pCR may indicate a favourable response to systemic therapy, at this time, it should not be interpreted as sufficient evidence of complete eradication of tumour cells to justify omission of radiation therapy. The Assisi think tank approach [14] including the post-hoc analysis of the DBCG IMN2 trial assist in identifying high risk patients for local recurrence that may benefit from a tumour bed boost [20]. However, the need for a tumour bed boost following pCR warrants further investigation in prospective trials or cohorts to balance between its potential benefits and harms. In these, radiation therapy should be reported according to recommendations like those provided by the European Society for Radiotherapy and Oncology (ESTRO) to generate high-quality data to further optimize treatment [21].

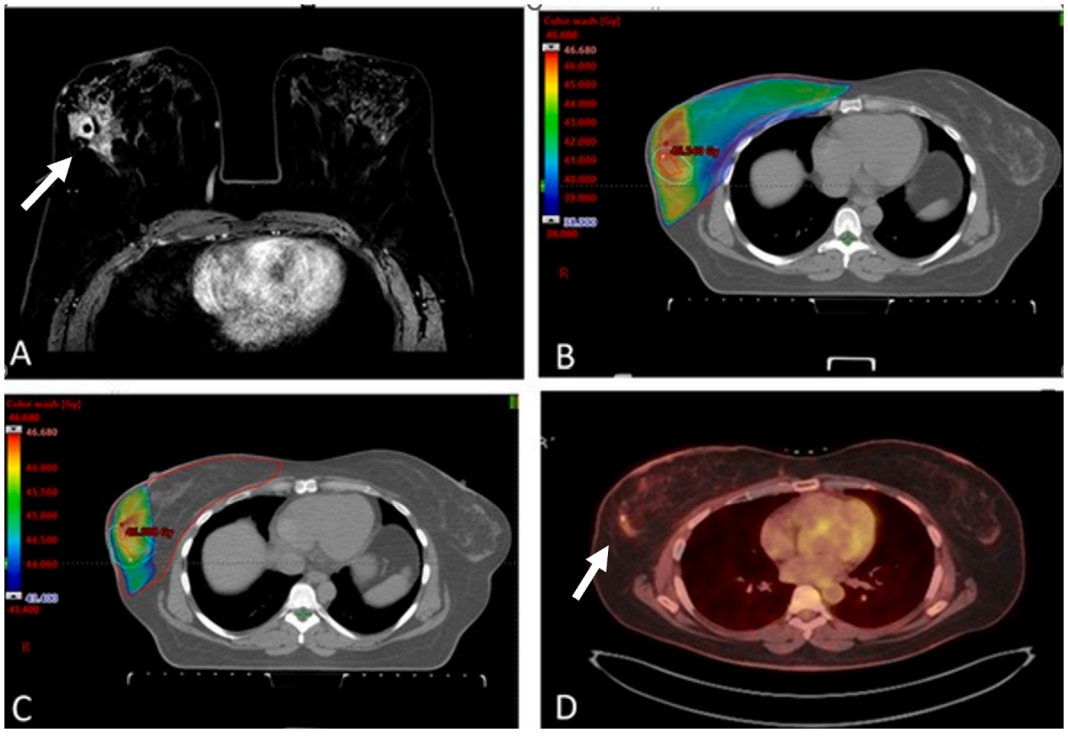

Fig. 1. A 46-year-old woman diagnosed with right breast cancer: cT3 (6 cm), N0, triple-negative, grade 3, Ki-67 90 %. She received PST including immunotherapy. Imaging suggested no residual disease, and she subsequently underwent breast-conserving surgery and sentinel lymph node biopsy, with final pathology ypT0N0 (0/2). The gross description of the lumpectomy specimen including the fibrotic tumour bed was 4.5 × 4 × 3.5 cm, with additional surgical extensions (of 2 cm diameter) in addition to the lumpectomy specimen in five directions. The patient continued immunotherapy and received postoperative whole breast irradiation (40.05 Gy in 15 fractions, over 3 weeks), with a simultaneous integrated boost (SIB) to a total dose of 45.75 Gy. Six months after completing radiation therapy (and four months after completing immunotherapy), she developed a local recurrence within the high-dose boost volume. A) T1-weighted gadolinium-enhanced breast MRI at the time of initial diagnosis (arrow pointing to the tumour); B) whole breast irradiation plan including a simultaneous integrated boost; C) boost volume coverage with 95 % of the prescribed dose; D) PET FDG-CT at the time of local recurrence (arrow pointing to the tumour).

CRediT authorship contribution statement

Orit Kaidar-Person: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Philip Poortmans:** Writing – review & editing, Supervision. **Icro Meattini:** Writing – review & editing, Supervision. **Trine Tramm:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110962.

Data availability

Data will be made available on request.

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