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Abstract: Preoperative breast radiation therapy (RT) is not a new concept, but older studies failed to change practice. More recently, there has been interest in revisiting pre-operative RT using modern techniques. This current perspective discusses the indications, summarises the published literature and then highlights current clinical trials, with particular attention to combining with novel drugs and optimising associated translational research.

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25th May 2017

Dear Professor Eggermont

RE: Re-submission of revised manuscript - Preoperative breast radiation therapy: indications and perspectives

We have re-submitted our revised manuscript as requested and we feel that this has been improved as a result of the reviewer's helpful comments. Thank you for consideration.

We have also acknowledged Dr Orit Kaidar-Person, as she has provided the source image for figure 1. and has given us permission to use it. We have also added a reference for this, which includes Dr Kaidar-Person's similar, but subtly different image. As these are different images, we do not think this would infringe copyright, but we would be grateful of your advice.

Yours sincerely

Dr Sara Lightowlers, on behalf of co-authors
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13th May 2017

Dear Professor Eggermont

RE: Submission of manuscript - Preoperative breast radiation therapy: indications and perspectives

We read with great interest the following very topical articles in your journal:

Riet, F. G. et al. Preoperative radiotherapy in breast cancer patients: 32 years of follow-up. Eur. J. Cancer 76, S62–S69 (2017).

Coles CE, Fourquet A, Poortmans P. Preoperative radiation therapy: The 'new' targeted breast cancer treatment? Eur. J. Cancer 78:116-117 (2017).

These have stimulated us to write the attached manuscript in the form of a Current Perspective, which explores the subject of preoperative radiotherapy further, including novel research trials. All the co-authors have contributed to the manuscript and have reviewed the final version. We would be grateful if you could consider this for publication please.

Yours sincerely

Dr Sara Lightowlers, on behalf of co-authors
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European Journal of Cancer
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Title of Manuscript:

PREOPERATIVE BREAST RADIATION THERAPY: INDICATIONS AND PERSPECTIVES

Contribution	**Author(s)**
Study concepts:	CHARLOTTE COLES
Study design:	CHARLOTTE COLES, SARA LIGHTOWLERS
Data acquisition:	N/A
Quality control of data and algorithms:	N/A
Data analysis and interpretation:	N/A
Statistical analysis:	N/A
Manuscript preparation:	SARA LIGHTOWLERS, CHARLOTTE COLES
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"I confirm that all the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *European Journal of Cancer*".

Signed (corresponding author): 
Date: 13/05/2017

***Revision Notes**

Response to reviewer's comments

Reviewer 1:

This review article is a contribution which was actually badly needed and will be extremely useful to the multidisciplinary teams involved in the therapeutic management of breast cancer. The presentation of the available data is clear. The whole field of this type of approach is covered by the authors. The conclusions are supported by the datasets provided in this manuscript.

We thank the reviewer for his/her encouraging comments.

An added value could result from the addition of:

- a short description, with relevant literature references, of the various innovative radiotherapy techniques which are used nowadays to fulfill the requirements of optimal delivery for neoadjuvant RT in breast cancer.

We agree that this would be a helpful addition to the manuscript and have added details of the RT techniques to Table 2 (new studies). In addition, we have added the following sentence to the introduction:

"However, there have been considerable advances in breast RT, including intensity modulated RT (IMRT), accelerated partial breast irradiation (APBI), simultaneous integrated boost and (SIB) and image guided radiation (IGRT) that could facilitate preoperative RT.**"**

- beyond the purely descriptive review of the literature data in this domain, more emphasis on which indications the authors really favour should be put in a discussion.

We have added the following sentence to the conclusion to address this:

"It is too early to speculate on the mature outcomes of these initiatives, but the authors of this review support investigation of all these approaches within the context of well designed clinical studies.**"**

***Highlights**

- Preoperative breast radiation therapy (RT) is being investigated in current trials
- RT could potentially downstage larger hormone receptor positive breast cancers
- Delivering RT before mastectomy and reconstruction may avoid sequencing difficulties
- Preoperative partial breast irradiation could be advantageous to cosmetic outcome
- Preoperative RT enables translational research included in current trial protocols

Preoperative breast radiation therapy: indications and perspectives

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Abstract

Preoperative breast radiation therapy (RT) is not a new concept, but older studies failed to change practice. More recently, there has been interest in revisiting pre-operative RT using modern techniques. This current perspective discusses the indications, summarises the published literature and then highlights current clinical trials, with particular attention to combining with novel drugs and optimising associated translational research.

206~~00~~ words (excluding abstract)

Introduction

Postoperative radiation therapy (RT) is indicated for most patients diagnosed with early breast cancer. However, conventional scheduling of breast cancer treatment is changing with increasing recognition of advantages of primary systemic therapy. Preoperative RT, although investigated in the past, was not demonstrated to be sufficiently advantageous for adoption into common practice. However, there have been considerable advances in breast RT, including intensity modulated RT (IMRT), accelerated partial breast irradiation (APBI), simultaneous integrated boost and (SIB) and image guided radiation (IGRT) that could facilitate preoperative RT. I~~i~~n this~~e~~ modern setting, preoperative RT may be useful in certain situations, which are discussed: (i) downstaging to enable conservation surgery, (ii) facilitating breast reconstruction, (iii) facilitating partial breast irradiation, and (iv) aiding translational research.

- **Downstaging of the tumour to enable conservative surgery**

Compared to mastectomy, women who undergo breast conserving surgery have significantly better body image and long-term quality of life scores[1]. For women with too locally advanced disease for breast conserving surgery, it may be possible to downstage the tumour with primary chemotherapy[2]. However, pathological complete response is less likely obtained with chemotherapy in luminal A disease and lobular carcinoma[3], than in other subtypes. These women are less likely to undergo conservative surgery following chemotherapy[3]. Primary endocrine therapy may be an option for these patients, but this practice is still relatively uncommon and is usually reserved for unfit patients with short life expectancies. An

alternative strategy for women with larger, hormone receptor positive and lower grade, breast cancers, could be preoperative RT. This could also be considered as salvage treatment for those who have responded less than anticipated to primary systemic treatment.

A number of older case series and single arm trials report on preoperative RT with or without concomitant chemotherapy[4–19] (Table 1). In those that report on receptor status, hormone receptor positive tumours were less likely to achieve pathological complete response to chemoradiation (chemoRT) than other subtypes[16,17], which is unsurprising given the better complete pathological response rates following chemotherapy for higher risk subgroups.

Those reporting on complications in general found more acute toxicity than would be expected with modern postoperative breast RT. This is of concern as moderate/severe toxicity from preoperative chemoRT could delay surgery and may increase surgical complications. Past experience suggests minimum RT-surgery interval is 4-6 weeks to minimise complications. Potential contributing factors to the increased toxicity include concurrent chemotherapy, and RT protocols and techniques using higher total doses, and simple field-based techniques. Modern RT techniques may widen the therapeutic ratio: hypofractionated schedules using a lower total dose reduce acute toxicity compared with conventional schedules[20], intensity modulated RT[21] and simultaneous integrated boost[22] produce more homogeneous dose distributions and can reduce acute toxicity and improve long-term cosmesis. The NeoAPBI trial is exploiting these concepts by sequencing primary systemic therapy with accelerated partial breast RT in chemo-resistant cancers[23].

Patients with hormone receptor positive cancers may benefit from RT in combination with endocrine therapy, rather than chemotherapy. This combination has been trialed[24]; in the series reported by Bollet et al[24] (n=42) 63% underwent breast conserving surgery, while previously been judged ineligible for this. Patients underwent surgery at median 8 weeks following completion of RT. Possibly allowing more time for maximal tumour regression may increase breast conserving surgery rates further. Continued treatment with endocrine therapy may facilitate safely increasing this time period, which is investigated in the UK feasibility study Neo-RT.

- **Facilitating breast reconstruction**

Despite the possibilities for downstaging to enable breast-conserving surgery, some patients will need or choose a mastectomy. Many of these patients will also require postmastectomy RT and may choose to have breast reconstruction. Scheduling of these treatments is challenging, since adding RT to a reconstruction results in a higher complication rate[25]. Most guidelines currently recommend RT prior to reconstruction[26]. However, this requires two separate surgeries, and there will be a delay before reconstruction can be performed. Patient satisfaction and quality of life may be improved by immediate reconstruction following mastectomy[27].

- ***Current practice for breast reconstruction and radiotherapy***

There are several challenges involved in delivering RT following breast reconstruction. Firstly, postoperative healing may cause delay of RT, which could impact on oncological outcomes. RT delivery is also potentially more difficult due to shape and consistency of the reconstructed breast, especially in case of implant reconstruction. Therefore, it may be impossible to obtain required coverage of the target whilst respecting dose constraints to organs at risk, resulting in a suboptimal plan (see Figure 1).

The current evidence is very limited as there are no randomised trials addressing RT timing and reconstruction and most series are small and retrospective. A large prospective cohort study has been reported by the Mastectomy Reconstruction Outcome Consortium, consisting of 175 patients receiving autologous reconstruction and chest wall RT (108 and 67 with immediate versus delayed reconstruction respectively)[28]. This showed no difference in complication rates, but lower levels of prereconstruction patient satisfaction in the delayed group, although satisfaction at one and two years postoperatively was comparable.

An insurance claims-base series of 4781 women who had undergone mastectomy and reconstruction (80% with implant-based) and RT showed that patients with irradiated implant reconstructions had twice the odds of having a complication and 11 times the odds of failure compared with irradiated autologous reconstruction[29]. The highest probability of implant failure was for RT followed by

delayed implant reconstruction, whereas the lowest was for immediate autologous reconstruction and postoperative RT.

In summary, it appears that delayed implant–based reconstruction after RT carries the greatest side effects, despite possible advantages for technical RT delivery before reconstruction. In comparison, toxicity is less with autologous reconstructions, but optimal timing of RT is unclear.

- ***Feasibility of RT prior to mastectomy and reconstruction***

  Preoperative RT delivery, followed by mastectomy and immediate breast reconstruction may avoid the difficulties described, whilst allowing women to benefit from having both surgical steps as one procedure. This sequencing has been described in a number of case series, reviewed by Tansley et al[30] in 2013, who conclude that oncological outcomes are comparable to standard sequencing. However, little published evidence was available at the time of review regarding complication rate. A further series of 111 patients published 2016[31] reported a rate of primary complications similar to that expected with standard sequencing.

  In the UK, the PRADA non-randomised interventional trial will evaluate safety and long-term cosmetic outcome of reversing the order of mastectomy with immediate reconstruction, with surgery 2-6 weeks after RT.

- **Facilitating partial breast irradiation**

  It is hypothesised that, in appropriately selected low risk patients, local relapse rates with partial breast irradiation will be comparable to whole breast RT, and reduced irradiated volumes will decrease toxicity. A meta-analysis of published results of reported trials to date[32] does not support this. However, the number of trials included is limited, and there are several large randomised trials yet to report. Preoperative rather than postoperative partial breast irradiation may be advantageous.

  Oncoplastic techniques can result in difficulty defining the postoperative tumour bed; even if surgical clips are inserted as they can be dispersed throughout the

breast (see Figure 2[33]). The tumour bed anticipated from the preoperative imaging, and the site of the actual target volume, may be significantly different[34]. The high interobserver variability reported amongst oncologists delineating the clinical target volume for postoperative partial breast irradiation[35] suggests difficulty ensuring the tumour bed is accurately targeted. Preoperative RT may reduce the risk of geographic miss, and preoperative imaging has been demonstrated to correlate with pathological size[36].

It has been shown that the partial breast clinical target volume may be increased by presence of postoperative seroma[37], and seroma size was an independent predictor of poor cosmesis in RAPID[38]. Preoperative partial breast RT would avoid this issue as well. Treatment volumes in the PAPBI trial of preoperative accelerated partial breast RT were significantly smaller (mean PTV 122cm^3) than those in postoperative partial breast RT studies with comparable mean tumour size[39] (mean PTV 296cm^3 in the study by Hepel et al[40]). In addition, the tissue receiving the highest radiation dose will be removed at surgery following preoperative partial breast RT.

- ***Current preoperative partial breast irradiation studies***

  First results of the PAPBI trial have now been published: cosmetic outcome was assessed as being good or excellent in 88, 89 and 100% of the 70 patients at 1, 2 and 3 years respectively[39]. For comparison, cosmesis was rated good/excellent in 71% at 3 years in RAPID[41]. At this early time point, efficacy is difficult to comment on and further results are awaited. In addition, the PAPBI-2 randomised phase III trial opened September 2016[42].

- **Facilitating translational studies**

  Following the approach of trials of primary systemic treatments, preoperative RT studies could facilitate translational research by assessing the effect of radiation directly on the tumour. Opportunities to study response to RT in humans are giving more reliable information compared to animal models. For example, it has proved difficult to produce hormone receptor positive patient-derived xenograft models, and to investigate the effects of a competent immune system[43]. This is particularly relevant considering RT studies, which are especially challenging following the low

local relapse rates, requiring recruitment of very large patient numbers and longterm follow-up, to demonstrate an effect.

- ***Assessment of tumour/normal tissue biology***

  Obtaining tissue samples before and after preoperative RT could facilitate research on the effects of radiation on both tumour and normal tissues. Greater understanding of biological effects of RT on breast tissue may increase the scope for personalisation of RT. Research of this nature is currently planned in trials of preoperative RT. A secondary goal of the PAPBI trial, alongside the PROBI trial of preoperative whole breast RT[44], is to develop a gene expression classifier predictive of radiosensitivity[39]. Neo-RT and Trans-PRADA will perform exploratory translational research into potential molecular biomarkers of response and into radiation-induced immune modulation.

- ***Assessment of RT/drug combinations***

  There is an unmet need for novel RT-drug combinations[45]. Although many targeted anticancer agents are now in use, little progress has been made identifying those that will synergise most effectively with RT[46]. The UK National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group have released a consensus statement that assessment of combination with RT should be part of the design of early phase studies in 'cases with a good biological and therapeutic rationale'[45]. For patients with triple negative breast cancer, the upcoming phase 1 RadioPARP trial[47] will investigate combination of the PARP inhibitor olaparib with RT either preoperatively, or as salvage following incomplete response after primary systemic treatment. This exploits the "BRCAness" trait in many of these tumours, with BRCA1 dysfunction causing DNA repair deficiency.

  'Window of opportunity' designs are now explored in 'phase 0' trials to expedite identification of active agents, with the advantage that tissue samples are obtained before and after the treatment of interest and can assess the effects of agents in treatment-naïve patients. Further along the drug development pathway, trialling RT/drug combinations in the preoperative setting could facilitate seamless phase II/III trial design, using pathological complete response as an intermediate biomarker. A recent phase 1b trial reported 25% pathological complete response

rate with PARP inhibitor veliparib added to preoperative RT and capecitabine in rectal cancer[48]; a combination that will be continued in an expanded cohort.

- ***Imaging biomarkers***

  The ability to assess prognostic and predictive tumour variables non-invasively in clinical practice is clearly advantageous, however, progress in validating novel imaging biomarkers for use in clinical practice has been slow. Studies of preoperative therapy have advantages for imaging biomarker validation, permitting correlation of imaging features before and during preoperative therapy with pathological/molecular endpoints. Increased ability to assess tumour biology with imaging could in turn facilitate adaptive RT, using strategies such as dose painting, individualised dose and fractionation schedules and combinations with targeted agents.

- **Conclusion**

  Conventional scheduling in breast cancer treatment has been challenged in recent years with primary systemic therapy now widely used. The potential advantages of delivering RT before surgery are now under investigation, with current and upcoming trials aimed at establishing its role in downstaging to enable conservative surgery and facilitating breast reconstruction and partial breast irradiation. Associated translational research may increase our knowledge of radiation effects in breast cancer and tumour tissue biology, facilitate discovery and validation of biological/imaging biomarkers and ultimately optimise novel drug-radiation combinations. It is too early to speculate on the mature outcomes of these initiatives, but the authors of this review support investigation of all these approaches within the context of well designed clinical studies.

Conflicts of interest: None

Acknowledgements

The authors are grateful to Dr Orit Kaidar-Person for providing the image used in Figure 1.

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Dr Birgitte V Offersen is supported by the Danish Cancer Society

Dr Youlia M. Kirova declares no grants support

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Dr Navita Somaiah is supported by NHS funding to the NIHR Biomedical Research Centre at The Royal Marsden and The Institute of Cancer Research.

Figure legends

Figure 1 shows a transverse section through a computed tomography (CT) radiation therapy planning scan for a patient with bilateral implant reconstructions. This demonstrates the challenge to irradiate the chest wall adequately without including unacceptable volumes of normal tissue, such as heart, lung and contralateral chest wall. Image provided by Dr O. Kaidar-Person.

Figure 2 shows the surface rendered image of the CT radiation therapy planning scan for a patient who has undergone oncoplastic breast conservation surgery[33]. The red markers represent widely scattered tumour bed surgical clips, which may result in a larger boost volume.

Footnotes

1. The list of trials of preoperative radiotherapy in table 2 was compiled through a combination of literature search, search of clinicaltrials.gov, and personal communication.

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Preoperative breast radiation therapy: indications and perspectives

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Abstract

Preoperative breast radiation therapy (RT) is not a new concept, but older studies failed to change practice. More recently, there has been interest in revisiting pre-operative RT using modern techniques. This current perspective discusses the indications, summarises the published literature and then highlights current clinical trials, with particular attention to combining with novel drugs and optimising associated translational research.

2066 words (excluding abstract)

Introduction

Postoperative radiation therapy (RT) is indicated for most patients diagnosed with early breast cancer. However, conventional scheduling of breast cancer treatment is changing with increasing recognition of advantages of primary systemic therapy. Preoperative RT, although investigated in the past, was not demonstrated to be sufficiently advantageous for adoption into common practice. However, there have been considerable advances in breast RT, including intensity modulated RT (IMRT), accelerated partial breast irradiation (APBI), simultaneous integrated boost and (SIB) and image guided radiation (IGRT) that could facilitate preoperative RT. In this modern setting, preoperative RT may be useful in certain situations, which are discussed: (i) downstaging to enable conservation surgery, (ii) facilitating breast reconstruction, (iii) facilitating partial breast irradiation, and (iv) aiding translational research.

- **Downstaging of the tumour to enable conservative surgery**

  Compared to mastectomy, women who undergo breast conserving surgery have significantly better body image and long-term quality of life scores[1]. For women with too locally advanced disease for breast conserving surgery, it may be possible to downstage the tumour with primary chemotherapy[2]. However, pathological complete response is less likely obtained with chemotherapy in luminal A disease and lobular carcinoma[3], than in other subtypes. These women are less likely to undergo conservative surgery following chemotherapy[3]. Primary endocrine therapy may be an option for these patients, but this practice is still relatively uncommon and is usually reserved for unfit patients with short life expectancies. An

alternative strategy for women with larger, hormone receptor positive and lower grade, breast cancers, could be preoperative RT. This could also be considered as salvage treatment for those who have responded less than anticipated to primary systemic treatment.

A number of older case series and single arm trials report on preoperative RT with or without concomitant chemotherapy[4–19] (Table 1). In those that report on receptor status, hormone receptor positive tumours were less likely to achieve pathological complete response to chemoradiation (chemoRT) than other subtypes[16,17], which is unsurprising given the better complete pathological response rates following chemotherapy for higher risk subgroups.

Those reporting on complications in general found more acute toxicity than would be expected with modern postoperative breast RT. This is of concern as moderate/severe toxicity from preoperative chemoRT could delay surgery and may increase surgical complications. Past experience suggests minimum RT-surgery interval is 4-6 weeks to minimise complications. Potential contributing factors to the increased toxicity include concurrent chemotherapy, and RT protocols and techniques using higher total doses, and simple field-based techniques. Modern RT techniques may widen the therapeutic ratio: hypofractionated schedules using a lower total dose reduce acute toxicity compared with conventional schedules[20], intensity modulated RT[21] and simultaneous integrated boost[22] produce more homogeneous dose distributions and can reduce acute toxicity and improve long-term cosmesis. The NeoAPBI trial is exploiting these concepts by sequencing primary systemic therapy with accelerated partial breast RT in chemo-resistant cancers[23].

Patients with hormone receptor positive cancers may benefit from RT in combination with endocrine therapy, rather than chemotherapy. This combination has been trialed[24]; in the series reported by Bollet et al[24] (n=42) 63% underwent breast conserving surgery, while previously been judged ineligible for this. Patients underwent surgery at median 8 weeks following completion of RT. Possibly allowing more time for maximal tumour regression may increase breast conserving surgery rates further. Continued treatment with endocrine therapy may facilitate safely increasing this time period, which is investigated in the UK feasibility study Neo-RT.

- **Facilitating breast reconstruction**

Despite the possibilities for downstaging to enable breast-conserving surgery, some patients will need or choose a mastectomy. Many of these patients will also require postmastectomy RT and may choose to have breast reconstruction. Scheduling of these treatments is challenging, since adding RT to a reconstruction results in a higher complication rate[25]. Most guidelines currently recommend RT prior to reconstruction[26]. However, this requires two separate surgeries, and there will be a delay before reconstruction can be performed. Patient satisfaction and quality of life may be improved by immediate reconstruction following mastectomy[27].

- ***Current practice for breast reconstruction and radiotherapy***

There are several challenges involved in delivering RT following breast reconstruction. Firstly, postoperative healing may cause delay of RT, which could impact on oncological outcomes. RT delivery is also potentially more difficult due to shape and consistency of the reconstructed breast, especially in case of implant reconstruction. Therefore, it may be impossible to obtain required coverage of the target whilst respecting dose constraints to organs at risk, resulting in a suboptimal plan (see Figure 1).

The current evidence is very limited as there are no randomised trials addressing RT timing and reconstruction and most series are small and retrospective. A large prospective cohort study has been reported by the Mastectomy Reconstruction Outcome Consortium, consisting of 175 patients receiving autologous reconstruction and chest wall RT (108 and 67 with immediate versus delayed reconstruction respectively)[28]. This showed no difference in complication rates, but lower levels of prereconstruction patient satisfaction in the delayed group, although satisfaction at one and two years postoperatively was comparable.

An insurance claims-base series of 4781 women who had undergone mastectomy and reconstruction (80% with implant-based) and RT showed that patients with irradiated implant reconstructions had twice the odds of having a complication and 11 times the odds of failure compared with irradiated autologous reconstruction[29]. The highest probability of implant failure was for RT followed by

delayed implant reconstruction, whereas the lowest was for immediate autologous reconstruction and postoperative RT.

In summary, it appears that delayed implant–based reconstruction after RT carries the greatest side effects, despite possible advantages for technical RT delivery before reconstruction. In comparison, toxicity is less with autologous reconstructions, but optimal timing of RT is unclear.

- ***Feasibility of RT prior to mastectomy and reconstruction***

  Preoperative RT delivery, followed by mastectomy and immediate breast reconstruction may avoid the difficulties described, whilst allowing women to benefit from having both surgical steps as one procedure. This sequencing has been described in a number of case series, reviewed by Tansley et al[30] in 2013, who conclude that oncological outcomes are comparable to standard sequencing. However, little published evidence was available at the time of review regarding complication rate. A further series of 111 patients published 2016[31] reported a rate of primary complications similar to that expected with standard sequencing.

  In the UK, the PRADA non-randomised interventional trial will evaluate safety and long-term cosmetic outcome of reversing the order of mastectomy with immediate reconstruction, with surgery 2-6 weeks after RT.

- **Facilitating partial breast irradiation**

  It is hypothesised that, in appropriately selected low risk patients, local relapse rates with partial breast irradiation will be comparable to whole breast RT, and reduced irradiated volumes will decrease toxicity. A meta-analysis of published results of reported trials to date[32] does not support this. However, the number of trials included is limited, and there are several large randomised trials yet to report. Preoperative rather than postoperative partial breast irradiation may be advantageous.

  Oncoplastic techniques can result in difficulty defining the postoperative tumour bed; even if surgical clips are inserted as they can be dispersed throughout the

breast (see Figure 2[33]). The tumour bed anticipated from the preoperative imaging, and the site of the actual target volume, may be significantly different[34]. The high interobserver variability reported amongst oncologists delineating the clinical target volume for postoperative partial breast irradiation[35] suggests difficulty ensuring the tumour bed is accurately targeted. Preoperative RT may reduce the risk of geographic miss, and preoperative imaging has been demonstrated to correlate with pathological size[36].

It has been shown that the partial breast clinical target volume may be increased by presence of postoperative seroma[37], and seroma size was an independent predictor of poor cosmesis in RAPID[38]. Preoperative partial breast RT would avoid this issue as well. Treatment volumes in the PAPBI trial of preoperative accelerated partial breast RT were significantly smaller (mean PTV 122cm^3) than those in postoperative partial breast RT studies with comparable mean tumour size[39] (mean PTV 296cm^3 in the study by Hepel et al[40]). In addition, the tissue receiving the highest radiation dose will be removed at surgery following preoperative partial breast RT.

- ***Current preoperative partial breast irradiation studies***

  First results of the PAPBI trial have now been published: cosmetic outcome was assessed as being good or excellent in 88, 89 and 100% of the 70 patients at 1, 2 and 3 years respectively[39]. For comparison, cosmesis was rated good/excellent in 71% at 3 years in RAPID[41]. At this early time point, efficacy is difficult to comment on and further results are awaited. In addition, the PAPBI-2 randomised phase III trial opened September 2016[42].

- **Facilitating translational studies**

  Following the approach of trials of primary systemic treatments, preoperative RT studies could facilitate translational research by assessing the effect of radiation directly on the tumour. Opportunities to study response to RT in humans are giving more reliable information compared to animal models. For example, it has proved difficult to produce hormone receptor positive patient-derived xenograft models, and to investigate the effects of a competent immune system[43]. This is particularly relevant considering RT studies, which are especially challenging following the low

local relapse rates, requiring recruitment of very large patient numbers and longterm follow-up, to demonstrate an effect.

- ***Assessment of tumour/normal tissue biology***

  Obtaining tissue samples before and after preoperative RT could facilitate research on the effects of radiation on both tumour and normal tissues. Greater understanding of biological effects of RT on breast tissue may increase the scope for personalisation of RT. Research of this nature is currently planned in trials of preoperative RT. A secondary goal of the PAPBI trial, alongside the PROBI trial of preoperative whole breast RT[44], is to develop a gene expression classifier predictive of radiosensitivity[39]. Neo-RT and Trans-PRADA will perform exploratory translational research into potential molecular biomarkers of response and into radiation-induced immune modulation.

- ***Assessment of RT/drug combinations***

  There is an unmet need for novel RT-drug combinations[45]. Although many targeted anticancer agents are now in use, little progress has been made identifying those that will synergise most effectively with RT[46]. The UK National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group have released a consensus statement that assessment of combination with RT should be part of the design of early phase studies in 'cases with a good biological and therapeutic rationale'[45]. For patients with triple negative breast cancer, the upcoming phase 1 RadioPARP trial[47] will investigate combination of the PARP inhibitor olaparib with RT either preoperatively, or as salvage following incomplete response after primary systemic treatment. This exploits the "BRCAness" trait in many of these tumours, with BRCA1 dysfunction causing DNA repair deficiency.

  'Window of opportunity' designs are now explored in 'phase 0' trials to expedite identification of active agents, with the advantage that tissue samples are obtained before and after the treatment of interest and can assess the effects of agents in treatment-naïve patients. Further along the drug development pathway, trialling RT/drug combinations in the preoperative setting could facilitate seamless phase II/III trial design, using pathological complete response as an intermediate biomarker. A recent phase 1b trial reported 25% pathological complete response

rate with PARP inhibitor veliparib added to preoperative RT and capecitabine in rectal cancer[48]; a combination that will be continued in an expanded cohort.

- ***Imaging biomarkers***

  The ability to assess prognostic and predictive tumour variables non-invasively in clinical practice is clearly advantageous, however, progress in validating novel imaging biomarkers for use in clinical practice has been slow. Studies of preoperative therapy have advantages for imaging biomarker validation, permitting correlation of imaging features before and during preoperative therapy with pathological/molecular endpoints. Increased ability to assess tumour biology with imaging could in turn facilitate adaptive RT, using strategies such as dose painting, individualised dose and fractionation schedules and combinations with targeted agents.

- **Conclusion**

  Conventional scheduling in breast cancer treatment has been challenged in recent years with primary systemic therapy now widely used. The potential advantages of delivering RT before surgery are now under investigation, with current and upcoming trials aimed at establishing its role in downstaging to enable conservative surgery and facilitating breast reconstruction and partial breast irradiation. Associated translational research may increase our knowledge of radiation effects in breast cancer and tumour tissue biology, facilitate discovery and validation of biological/imaging biomarkers and ultimately optimise novel drug-radiation combinations. It is too early to speculate on the mature outcomes of these initiatives, but the authors of this review support investigation of all these approaches within the context of well designed clinical studies.

Conflicts of interest: None

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Figure legends

Figure 1 shows a transverse section through a computed tomography (CT) radiation therapy planning scan for a patient with bilateral implant reconstructions. This demonstrates the challenge to irradiate the chest wall adequately without including unacceptable volumes of normal tissue, such as heart, lung and contralateral chest wall. Image provided by Dr O. Kaidar-Person.

Figure 2 shows the surface rendered image of the CT radiation therapy planning scan for a patient who has undergone oncoplastic breast conservation surgery[33]. The red markers represent widely scattered tumour bed surgical clips, which may result in a larger boost volume.

Footnotes

1. The list of trials of preoperative radiotherapy in table 2 was compiled through a combination of literature search, search of clinicaltrials.gov, and personal communication.

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Table 1

Author (year of publication)	Number of patients in study	Tumour characteristics	Total dose (dose per fraction)	Concomitant chemotherapy	Response	Locoregional complications
Semiglazov[4] (1994)	271	Clinical stage IIb-IIIa	60Gy (2Gy)	TMF*/none	pCR¶ rate 29.1% for those reciving concomitant chemotherapy; 19.4% radiotherapy alone	Not available
Touboul[5] (1996)	97	Non-inflammatory breast cancer; clinical stage IIIa-IIIc	45Gy (1.8Gy) 25-30Gy boost delivered in those patients not undergoing surgery (34%)	None	10 year locoregional control rate 80% (76% for those not undergoing surgery)	Not available
Skinner[6] (1997)	30	Non-inflammatory breast cancer; clinical stage IIb-IIIc	50Gy (2Gy)	5-fluorouracil	pCR rate 17%	30% moist desquamation
Colleoni[7] (1998)	23	Clinical T2-T4/N0-N1	50Gy (2Gy) 10Gy boost	None	pCR rate 8%; 80% underwent breast conserving surgery	Postoperative complications were 'frequent'
Skinner[8] (2000)	29	Clinical stage IIb-III	45Gy (1.8Gy)	Paclitaxel	pCR rate 26%	Not available
Calitchi[9] (2001)	75	Non-inflammatory breast cancer; clinical T2-3	45Gy (1.8Gy) 15Gy boost to internal mammary nodes	None	pCR rate 11%; locoregional control rate at median follow up 10 years 88%; 100% underwent breast conserving surgery	Not available
Formenti[10] (2003)	44	Clinical stage IIb-III	45Gy (1.8Gy) 14Gy boost	Paclitaxel	pCR rate 16%; 93% underwent modified radical mastectomy	7% grade 3-4 skin toxicity
Lerouge[11] (2004)	120	Non-inflammatory breast cancer; clinical stage IIIa-IIIc	45Gy (1.8Gy) 25-30Gy boost delivered in those patients not undergoing surgery (32.5%)	None	15 year locoregional control rate 76.2%	Not available
Chakravarthy[12] (2006)	30	Clinical stage IIa-IIIb	46.8Gy (1.8Gy)	Paclitaxel	pCR rate 34%; 43% underwent breast conserving surgery	2 patients experienced grade 3-4 skin toxicity
Bollet[13,14] (2006; 2012)	60		50Gy (2Gy)	Vinorelbine and 5-fluorouracil	pCR rate 27%; 69% underwent breast conserving surgery	14% grade 3 skin toxicity
Shanta[15] (2008)	1117	Non-inflammatory	40Gy (2Gy)	CMF**/ECF†/FAC††	pCR rate 45.1%	'Deep pigmentation and

		breast cancer; clinical stage IIb-IIIb				mild to severe dry epidermis', with occasional moist desquamation
Alvarado-Miranda[16] (2009)	112	Clinical stage IIb-IIIb; 48% ER positive	50Gy (2Gy) 10Gy boost	MTCF‡/GC‡‡	pCR (primary and nodal) rate 29.5%	Not available
Adams[17] (2010)	105	Clinical stage IIb-IIIc; 52% ER positive	45Gy (1.8Gy) 14Gy boost	Paclitaxel +/- trastuzumab	pCR rate 34%; 5 year locoregional control rate 95.2%	Not available
Matuschek[18] (2012)	315	Clinical T1-T4/N0-N1	50Gy (2Gy) 10Gy boost +/- hyperthermia	EC§/CMF/AC§§/ mitoxantrone/ none	pCR (primary tumour and nodal) rate 29.2%	Not available
Riet[19] (2017)	187	Non-inflammatory breast cancer; clinical stage IIa-IIIb	45-55Gy (2.5Gy)	None	10% pCR rate; 30 year locoregional control rate 89%	19% 30 day postoperative complication rate; 4% grade 3-4 skin necrosis
	Table 1: Case series and trials reporting patients treated in the 1980s,1990s and early 2000s with preoperative breast radiotherapy or chemoradiotherapy. *TMF, thiotepa, methotrexate and 5-fluorouracil; **CMF, cyclophosphamide, methotrexate and 5-fluorouracil; †ECF, epirubicin, cyclophosphamide and 5-fluorouracil; ††FAC, 5-fluorouracil, doxorubicin and cyclophosphamide; ‡MTCF, mitomycin C and 5-fluorouracil; ‡‡GC, gemcitabine and cisplatin; §EC epirubicin and cyclophosphamide; §§AC, doxorubicin and cyclophosphamide; ¶pCR, pathological complete response.					

Table 2 (amendments highlighted)

Title	Type of study	Patient recruitment target	Study design	Primary endpoint	RT technique
PAPBI-2	Phase III randomis~~z~~ed trial	500 patients	Preoperative vs. postoperative accelerated partial breast irradiation	Cosmetic outcome, assessed by digital photographs, patient's questionnaires and specialist's questionnaires	Partial breast ~~VMAT or~~ IMRT 28.5Gy in 5 fractions over 1 week
NeoAPBI 01	Phase II randomis~~z~~ed trial	362 patients	Primary chemotherapy vs. primary chemotherapy and sequential APBI*	Breast pathological complete response rate	Partial breast 3D-conformal RT with either: 25Gy in 10 fractions twice a day over 5 days (maximum 8 days) or 25Gy in 8 fractions daily
PROBI	Phase I/II non-randomis~~z~~ed feasibility trial	94 patients	Preoperative whole breast radiation therapy	Postoperative complications	Breast (and regional lymph node) IMRT 46,2 Gy in 21 fractions over 4 weeks, with SIB*** ~~simultaneous integrated boost~~ to tumour to 55,86 Gy
NeoRT	Phase I non-randomis~~z~~ed feasibility trial	43 patients	Preoperative breast IMRT** followed by 20 weeks hormonal therapy prior to surgery	Proportion of patients successfully completing preoperative radiation therapy and hormonal therapy followed by breast surgery	Breast IMRT 40Gy in 15 fractions over 3 weeks, with ~~simultaneous integrated boost~~SIB to tumour to 48Gy
RadioPARP	Phase I trial	30 patients	Preoperative or postoperative radiation therapy with concurrent olaparib	Maximum tolerated dose of olaparib	Breast RT 50Gy in 25 daily fractions over 5 weeks; 46 Gy to nodal regions in 23 daily fractions over 4.6 weeks. SIB with IMRT to tumour can be considered.~~Conventional fractionation; all techniques allowed~~.
ABLATIVE	Non-randomis~~z~~ed interventional trial	25 patients	Single dose preoperative ablative radiation treatment; breast conserving surgery 6 months following completion.	Breast pathological complete response rate~~.~~	Partial b~~B~~reast IMRT~~VMAT~~, with SIB: single fraction~~1x~~ 15 Gy to PTV_{GTV} , ~~1x~~ 20 Gy to PTV_{GTV}
PRADA	Non-randomis~~z~~ed interventional trial	20 patients	Preoperative radiation therapy; mastectomy and DIEP† flap reconstruction 2-6 weeks following completion.	Presence of open breast wound at 4 weeks after mastectomy and DIEP flap reconstruction	Breast (and regional lymph node) IMRT 40Gy in 15 fractions over 3 weeks

Table 2: Novel trials involving preoperative radiation therapy currently in the set up phase, or recruiting patients (footnote 1). *APBI, accelerated partial breast irradiation; **IMRT, intensity modulated radiation therapy; †DIEP, deep inferior epigastric perforator~~;~~, ***SIB, simulta~~a~~neous integrated boost.~~.~~

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***Figure 1**

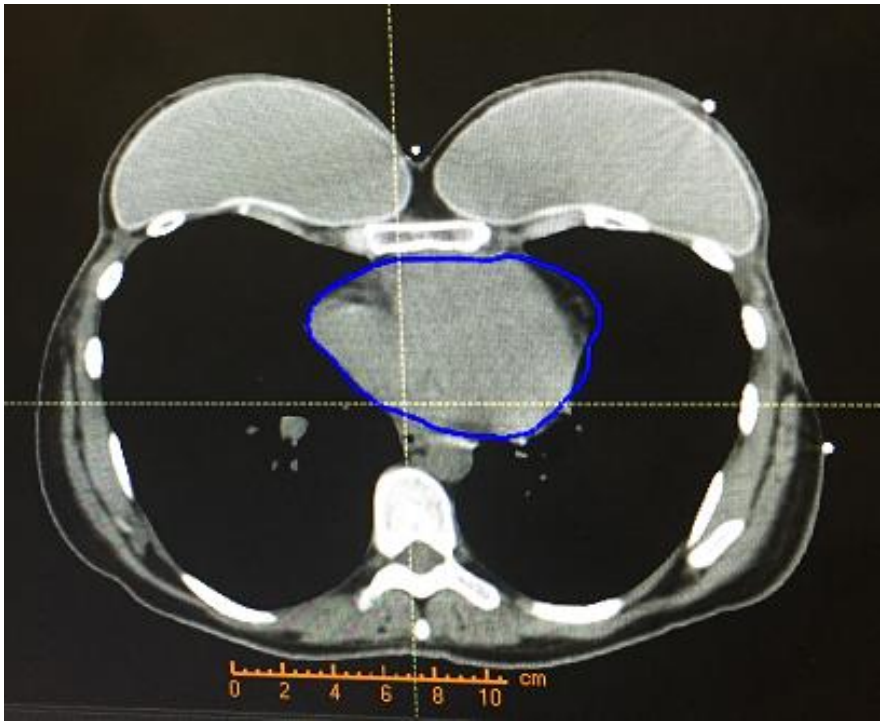

Figure 1

***Figure 2**

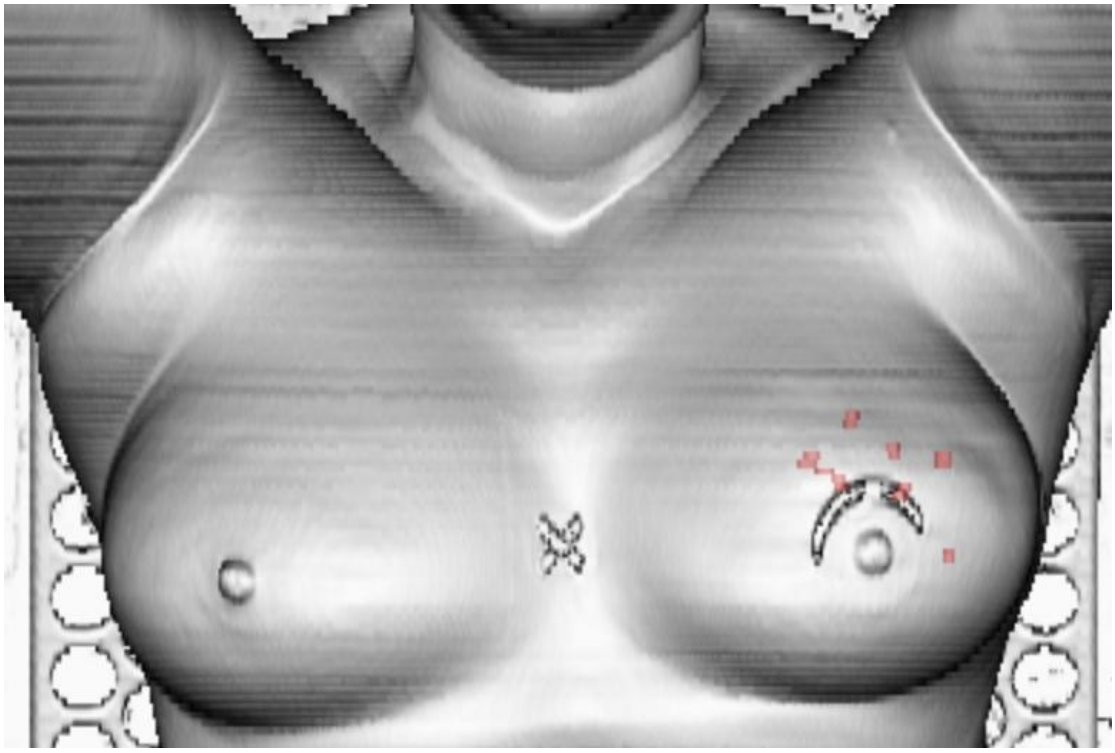

Figure 2

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