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GENERAL DISCUSSION

Radiotherapy is an integral part of breast conserving therapy. It substantially improves treatment efficacy by decreasing local recurrence rates and results in an increased breast cancer specific survival [1-6]. With the introduction of the planning CT scan over the last decades, it was possible to gather more precise information on both dose homogeneity in the target volume and mean and maximum dose in the organs at risk. In recent years the knowledge concerning the side effects of this radiation treatment has increased further and, amongst others, the effect on the heart was documented [7,8]. Based on this knowledge, important aspects of the treatment delivery have been changed in order to minimise the dose in the heart. Still, a number of unanswered questions remain and further improvements in the treatment delivery seem possible. In this thesis, several strategies to optimise the radiation treatment for patients with breast cancer were analysed. First, we focussed on optimising the target volume delineation. Subsequently, several treatment planning techniques were compared in order to decrease the dose to the heart. Also, with decreasing the dose in the heart, changes of calcium scores in the coronary arteries of the various patient categories were followed in the years after treatment.

Delineation of volumes in breast cancer radiotherapy

Optimal definition of the target is the first step in the radiation treatment process. Improperly defined target volumes may lead to a systematic geographic miss in the individual patient during the whole course of radiation treatment [9-11]. Ultimately, this may negatively affect the treatment efficacy and could also lead to an increased dose to organs at risk.
Several uncertainties, (e.g. positioning inaccuracies; technical inaccuracies), were defined influencing the efficacy of the radiation treatment. As was stated by several authors the inter-observer differences in delineating the target volume is a large uncertainty in the radiotherapy process [12,13]. These uncertainties can be defined by, for example the Conformity Index (CI), a tool for quantification of the variability of delineation. For the special circumstance where the number of observers equals two, it is defined as the volume of agreement divided by the total encompassing volume. This has been generalised to any number of observers by Kouwenhoven et al. [14]. This tool, the generalised CI (CIgen), was used in our delineation studies [15-17].

In breast conserving radiotherapy, the target volume delineation aims at delineating the glandular breast tissue (CTV Breast) and the Lumpectomy Cavity (LC). In order to improve the uniformity of the delineation of these structures the following measures seem relevant:

1. Use of guidelines;
2. Allocating breast cancer dedicated staff members.
3. Addition of MR images.

Ad 1: The use of guidelines improved the consistency of the target delineation [12,18,19], however, this was questioned by Van Mourik et al. They still reported considerable variation between observers despite the use of delineation guidelines for the LC [13]. Also, Boersma et al. stated that the interpretation of guidelines is the weakest link in the chain of delineating the LC, even when using a pre-operative CT scan [20]. Therefore, a dedicated team of radiation oncologists is necessary.

Ad 2: Radiation oncologists with expertise in breast cancer radiotherapy should consult each other when delineating the LC, since the interpretation of the LC is difficult and large differences exist. Several studies revealed that some observers delineate the target volume systematically larger or smaller than others [12,21]. As peer review of the delineated volumes might improve the consistency of delineating the target volume, and as the review by radiologists seems to be of importance, radiologists should be readily available for consultation [13]. Furthermore, consultation of radiologists improves the image interpretation and could also contribute to a better use of the optimal window/level settings in delineating the target volume.

Ad 3: Adding MR imaging may improve the visibility of the target volume [10]. Therefore, in our delineation studies we compared the delineation of the CTV Breast and the LC of 10 patients (delineated by two radiologists and two radiation oncologists) on both the CT and MR images separately and on the co-registered CT-MR images. In these studies the conformity indices were compared. However, in our study we found that adding MR images did not improve the consistency of the delineated volumes [15-17].

For the CTV Breast the largest variations were found in the medial and lateral borders of the target volume. Apart from the effect of these variations on the dose in the glandular breast tissue, Li et al. pointed out that these variations have the largest impact on the dose in the surrounding structures [22] and could thus increase the dose in the organs at risk (OAR). Another study analysing the additional value of using an MR imaging in target delineation of breast tissue also showed that the use of these images did not improve the consistency between observers [23], this is in line with our results.
Concerning the delineation of the LC, we found that the delineated volumes differ widely between observers. Also, the addition of MR images in these cases did not improve the consistency. A joint review of the delineated LC might provide a more consistent volume, and could avoid a geographic miss of the LC.

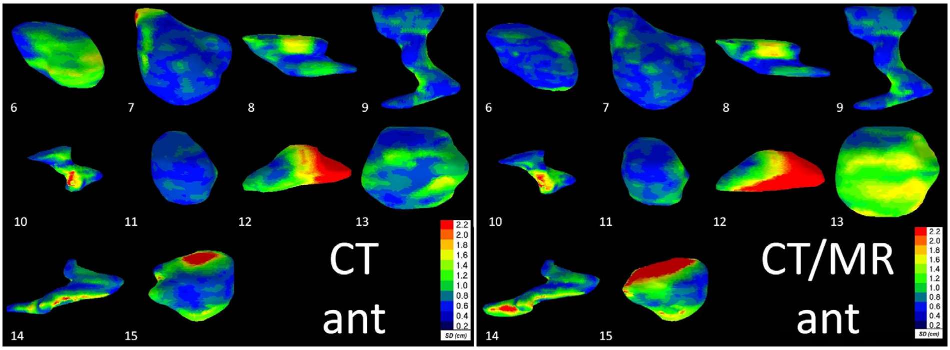

Figure 1. Coronal view of ten delineated lumpectomy cavity (LC) volumes in anterior and posterior view. Colour map: blue, high agreement between observers; red, low agreement between observers, according to the scale given.

In both CT and CT-MR delineated LC volumes we found a CI of roughly 0.50. To note is that delineation differences in small volumes (when compared to larger volumes) appear to have a large impact on the calculated CIs. Furthermore, registration of CT and MRI remains difficult due to respiratory motion artefacts, together with distortion of breast tissue by overlying MR receiver coils. We found that multimodality breast markers are obligatory in performing an optimal CT-MR registration [24]. Avoiding the adjustment of CT-MR registration manually is important since this influences the definite LC volumes [20].
Adding surgical clips is a prerequisite to determine the lumpectomy volume according to the systematic review of Yang et al. [10]. The surgical clips are visible on the CT scan

and can be used as a helping tool in delineating the LC. However, defining the LC with the use of clips appear to be difficult as well, since the clips represent only a few points of the LC's border and an interpolation is usually required, resulting in delineation inaccuracies [10].

Apart from the variations reported in delineating the target volumes, Lorenzen et al. also described that variations can be found when delineating the heart and the coronary arteries. The use of guidelines for delineation of the heart improved the consistency considerably. However the use of guidelines did not improve the consistency of the left anterior descending (LAD) coronary artery delineation, since the LAD was not visible on all CT slices [25]. Therefore, aiming at delineating the LAD region instead of the LAD itself seems more appropriate.

Future perspectives: delineation of volumes
Based on our study results we do not advise to use MR images in addition to the CT scan when delineating either the glandular breast tissue or the lumpectomy cavity. It was demonstrated that differences in the delineated volume had great impact on the dose in the OAR. Therefore, we strongly suggest the following procedure in the delineating process. Firstly, we recommend that each observer should take advantage of the full potential of the planning system. By using the CT information in all three projections the observer keeps a better overview of the delineated structures. As a second recommendation, we expect that implementation of auto-contouring in the clinic may further improve the consistency in the generated structures. But, still, the expected conformity in delineation of the lumpectomy cavity needs to be proven. Thirdly, the ability of the radiation therapists to delineate the glandular breast tissue could further increase the efficiency in a radiation therapy department [26]. However, we are aware that a shift in activities and responsibilities of the radiotherapy team needs to be implemented gradually.

Treatment planning techniques in breast cancer radiotherapy

Performing treatment planning studies
Treatment planning studies have proven their value. The results give insight into the pros and cons of the several available treatment techniques. The results can be used to decide whether a new technique should be used in daily practice [27]. However, in order to make a true comparison of the various techniques, it is essential to define the same initial conditions for each separate technique. Depending on the defined hypothesis either the level of target coverage can be set equally, and in doing so enable the evaluation of the dose in the OAR, or the doses in the OAR are set equally, allowing evaluation of the differences in target coverage for the various compared treatment techniques. Also, the level of details of the calculated treatment technique needs to be described extensively, e.g. in a supplementary Table, in order to maximise the usefulness of the described planning techniques [27]. This is certainly helpful to the radiotherapy staff enabling them to reproduce the described radiation technique. Consequently, both reviewer and the journal, to which the manuscript was submitted, need to take their responsibility in maintaining uniformity in the described treatment planning studies.

Apart from these treatment-planning studies in daily practice the radiation oncologist will approve the final treatment plan. But he or she may decide to compromise the planning target volume coverage to spare an OAR.

Sparing organs at risk in breast cancer radiotherapy

Contralateral breast cancer (CBC)
Some patients with breast cancer have an elevated risk of developing a second breast cancer in the contralateral breast after radiotherapy [28,29]. Especially women who are diagnosed with breast cancer at young age (younger than 35 years old) and with a family history of breast cancer or an oestrogen receptor negative primary tumour, have a higher incidence of contralateral breast cancer [30]. Furthermore, Stovall et al. stated that for young patients (younger than 40 years old) an increased risk was found for doses in the contralateral breast higher than 1 Gy [31]. Also, Hooning et al. calculated the CBC risk and found a hazard ratio of 1.23 on the risk of medial contralateral breast cancer when receiving a radiation dose to the medial part of the contralateral breast up to 3.6 Gy in women < 45 years old [32]. For each individual patient the radiation oncologist should always decide if a higher dose in the contralateral breast outweighs a higher dose in the heart and the LAD-region. Recently, Abo-Madyan et al. stated that the use of multiple beam IMRT or VMAT increases the risk of CBC, although the absolute risk was low. Tangential IMRT results in a lower CBC risk [33].

Heart and coronary arteries
It is important to always reduce the dose in the heart and coronary arteries as much as possible, since several studies state that a higher dose in these arteries is associated with an increased risk of cardiovascular disease [7,8,34,35]. Paszat et al. found a higher risk of anterior myocardial infarction when larger volumes of the heart were incorporated in the treatment fields [36]. Interestingly, radiation techniques have changed over time and have led to a reduced heart dose. Graham et al. investigated the dose differences before and after routine 3D planning or cardiac contouring (before and after contouring era). They reported a significant lower mean heart dose in low risk patients (without treatment of internal mammary nodes or a boost dose), but no difference in the mean LAD dose. However, a correlation was reported between the Maximum Myocardial Depth (MMD) and the LAD dose; the mean doses in the inferior part of the LAD increased from 49% to 84% of the prescribed breast dose when the MMD was >15 mm. They also identified a 15-mm MMD as a useful transition point from low to high mean inferior-LAD doses [37]. On the opposite Aznar et al. stated that the dose delivered to the coronary arteries and the dose delivered to the heart are not necessarily correlated and that both organs at risk need to be delineated in order to get proper information of the applied doses [38]. Delineating the LAD is, however, difficult, and as Vennarini et al. stated, only one-third of the artery could be objectively visualised [39]. Therefore, delineating an LAD-region, instead of just the LAD, would be more appropriate in order to avoid a misinterpretation of the received dose [40,41].

Lung
The Quantec tolerance guidelines provide organ-specific dose/volume/outcome data. For the lungs, a dose tolerance has been described to avoid radiation pneumonitis, i.e. the volume that receives 20 Gy needs to remain below 30% for both lungs [42]. Also, the risk of radiation induced secondary lung cancers was increased, especially after a long term follow up period of 20 years [43,44]. A recently published review clearly showed that the risk of second lung cancers after breast cancer radiotherapy increases gradually in time. A dose-response relation for lung cancer has also been described, indicating a risk that seems to increase linearly with 8.5% (95% CI 3.1% to 23.3%) per delivered Gy to the lung [44]. A nested case-control study by Grantzau et al. confirmed that this risk was enhanced in ever smokers, with an excess rate of 17.3% per Gy [45].

Treatment planning techniques in breast cancer radiotherapy
With IMRT the dose homogeneity is increased and a 3-7% decrease of hotspots can be achieved. Two phase-III trials demonstrated that women in the IMRT treatment arms had less acute toxicity, long-term telangiectasia and fibrosis compared to women irradiated with 3D-CRT techniques [46]. The phase-III trial of Donovan et al. points out that doses higher than 105% can result in more induration of the breast [47]. However, the used IMRT techniques were more complex than the tangential IMRT technique we currently use [47-50]. The authors of both trials concluded that an IMRT technique should specifically be used for patients with large breasts. Munshi et al. report the same findings, they advise to perform a 2D technique in patients with small breasts [51]. In our treatment planning studies we see a higher homogeneity when using tangential IMRT compared to a 3D-CRT technique; this tangential IMRT technique is less complex and succeeds to significantly lower the dose in the heart and LAD, regardless of the volume of the breast.
It is remarkable that Graham et al. did not find a significant reduction of the cardiac dose in a comparison study from 2D to 3D CT-treatment planning [37]. They reported that the inferior part of the LAD received a high mean dose which could be lowered by using a breath-hold technique. Aznar et al. confirmed this finding. They performed a study on the dose levels in the specific parts of the heart [38]. In our treatment planning comparison study we found that, when using an IMRT technique, the dose decreased, in the heart as well as in the LAD-region. Specifically the caudal part of the treatment fields, including the LAD, received a lower dose. We, therefore, concluded that an IMRT technique adds a substantial gain in lowering the dose, especially in the caudal part of the heart, and, hence, in the caudal part of the LAD.

Finally, in defining the most optimal radiotherapy treatment technique with the lowest heart dose, one must not forget that the heart moves in and out (to some degree) of the radiotherapy treatment fields. Several studies quantified the movement of the heart [52,53]. Wang et al. advised more than 5 mm of distance between the LAD and the field edge because of the motion of the heart itself [54]. These variations should be kept in mind when evaluating the radiotherapy treatment plans. Adding a margin around the critical structures could be helpful.

Future perspectives: treatment planning
As several studies have shown, it is important to avoid as much radiation dose as possible in the heart and coronary arteries. Epidemiological studies show that even low doses need to be avoided as well. Based on literature [45,55] and our study results we advise the following arbitrary constraints when performing radiotherapy in left-sided breast conserving radiotherapy, since no absolute thresholds could be defined. The constraints, we advice, appear to be feasible from our treatment planning studies (using a fractionation scheme of 42.56 Gy in 16 fractions):

1. Mean heart dose < 2 Gy;
2. Mean lung dose < 5 Gy;
3. Mean dose outside the PTV as low as reasonably achievable.
4. In patients younger than 45 years the dose in the contralateral breast should be as low as possible. In BRCA 1/2 carriers this is of even more importance.

We propose to perform a tangential IMRT technique in all patients, regardless of age and size of the breast, since in all studied patients an increase in dose homogeneity was found, as well as a reduction in dose in the heart, specifically in the caudal part of the treatment fields. By using a tangential IMRT technique the dose will better encompass

the target volume and the dose in the heart and LAD will be decreased as well. Moreover, when using a tangential IMRT technique no increase in the low dose regions in the normal tissue was found, even when applying a multiple beam IMRT technique.
Another important aspect of the radiation treatment is to achieve the lowest dose in the normal tissue outside the treatment fields. In our treatment planning studies the proton therapy technique results in the lowest dose in the heart and coronary arteries and would, therefore, be the treatment of choice. However, an increased risk of skin toxicity could be expected when using protons [56]. The used proton technique (i.e. using multiple proton beams instead of a single beam) or the use of scanning techniques, advances in patient positioning and fractionation schedules seem to be important in reducing the skin dose [56,57]. Furthermore, as yet, proton therapy is not available in the Netherlands. However, if a limited use of proton therapy would be available, we would recommend a comparative assessment between costs, toxicity and the urgency of a dose reduction.

Another option to reduce the dose in the surrounding structures is the Accelerated Partial Breast Irradiation (APBI) technique. To determine if a patient is eligible for an APBI technique guidelines are available (ASTRO and ESTRO guidelines) [58,59]. According to these guidelines a patient could be classified in the so called "low risk" group. APBI techniques are widely available and appear to be feasible. The lower number of fractions is convenient for the patient. Furthermore, aiming only at the lumpectomy cavity the dose in the heart is lower. This is specifically valid for Intra Operative Radiotherapy (IORT) since the dose in the surrounding structures remains low by using proper shielding.

Breath-hold techniques in left-sided breast cancer radiotherapy

When using the most optimal 3D conformal radiotherapy treatment technique in left-sided breast cancer to reduce the dose in the organs at risk, it became clear that the LAD coronary artery still could receive a relatively high maximum dose (2.7 Gy - 41.7 Gy; to note: some patients received nodal irradiation as well) [39]. We found that the mean LAD dose could be reduced with 50% when using a breath-hold technique, and for the high dose region this reduction was even larger. This was confirmed in other studies as well [60,61]. However, the randomised trial from Zellars et al. showed that ABC was not significantly associated with prevention of perfusion deficits compared before and six months after the radiation treatment. The reason that in four years time only 50 patients could be enrolled to this study remains unclear. Furthermore, a longer follow-up is needed to confirm their findings [62].

Several methods for performing a breath-hold technique are available, e.g. Active Breathing Control (ABC), voluntary breath-hold in combination with on-line registration of the patient position, Real-time Position Management system. [60,63-65]. The reproducibility of the various breath-hold methods was studied, all methods proved to be safe, including the ABC technique [66]. Recently Mittauer et al. investigated the dosimetric impact of breath-hold variations when using ABC. The estimated effect for the target coverage was negligible, however a large impact was estimated for the OARs [67]. One needs to consider this when applying breath-hold techniques. Most important is that the patient performs a moderate deep inspiration breath-hold (mDIBH) to achieve the largest distance between the heart and the radiation fields [68]. Remouchamps et al. defined a breath-hold threshold level of 75% of the maximum aspiratory capacity of the patient. The mDIBH level was chosen as a balance between achieving substantial heart displacement and maintaining patient comfort [68]. However, in a randomised cross-over study, the Royal Marsden found that a voluntary breath-hold and the ABC technique were comparable as regards the reproducibility and the dose in the OARs, but that patients and staff preferred the voluntary breath-hold technique. It remains unclear why 136 of the in total 159 patients were excluded from the study [69]. In the diversity of treatment planning techniques for some patients the heart dose appears to be low as well without breath-hold, see Figure 2. In these patients treatment without a breath-hold technique could be an option, especially since no threshold for the heart and LAD dose could be defined in the literature. Also, the introduction of an age restriction could be considered, although Darby et al. recently found that cardiac events were observed within just 5 years after the radiation treatment and were independent of age [8]. In our institution 98% of the patients were able to complete the active breathing control method [64]. Moreover, this method potentially enables a more individualised approach. Summarising, the ABC technique is a reproducible and reliable technique. Therefore, we decided to use this type of breath-hold technique in all patients. Recently, Register et al. confirmed that no specific anatomic surrogate for the dosimetric benefits of DIBH technique could be identified; only the heart volume in the treatment field predicted the reduction in mean heart dose. They stated that a breath-hold technique should be used for all patients receiving left-sided breast cancer irradiation [70].

The results of our planning studies (Figure 2) clearly show that the breath-hold technique significantly reduces both the dose in the heart and the LAD-region. From our treatment planning studies TomoTherapy in breath-hold, when compared to tangential IMRT in breath-hold, appears to add an extra dose reduction. Unfortunately, it is not possible yet to combine TomoTherapy with breath-hold in a clinical setting. Furthermore, the mean heart dose reduction when using the TomoTherapy technique is limited, 1.5Gy (SD 0.5Gy) for IMRT in breath-hold and 1.1Gy (SD 0.4Gy) for the TomoTherapy technique in breath-hold. Therefore, the most optimal treatment technique for left-sided breast cancer radiotherapy appears to be the tangential IMRT technique combined with a breath-hold technique.

Whether the use of a breath-hold technique reduces the risk of coronary heart disease cannot be confirmed, although our calcium score study revealed a positive effect. Three years after whole breast irradiation we found a significantly smaller increase of LAD calcium scores in the group irradiated using a breath-hold technique when compared to patients irradiated without the use of breath-hold. Specifically, the individual findings of the coronary artery calcium (CAC) score in each patient are important. When the RCA CAC score was subtracted from the LAD CAC score it became clear that in the group of left-sided breast cancer patients, treated with a breath-hold technique, a significantly smaller increase in CAC score was noted 3 years after whole breast irradiation. Therefore, the risk of cardiac heart disease may have decreased as well, since the amount of CAC scores predicts the risk of subsequent cardiovascular events [71,72]. Drawbacks of our study are the small numbers and the relatively short follow-up period.

Finally, in performing treatment-planning studies, guidelines need to be formulated in order to be able to compare the results of studies. The scientific journals could be helpful in designing these guidelines. In combination with the ICRU recommendations, guidelines for planning studies can be helpful to optimise the radiation treatment techniques in daily practice.

Future perspectives: breath-hold techniques

With the increased knowledge concerning the several applied breath-hold techniques, it seems that aiming at an optimal enlargement of the thoracic volume is of importance.

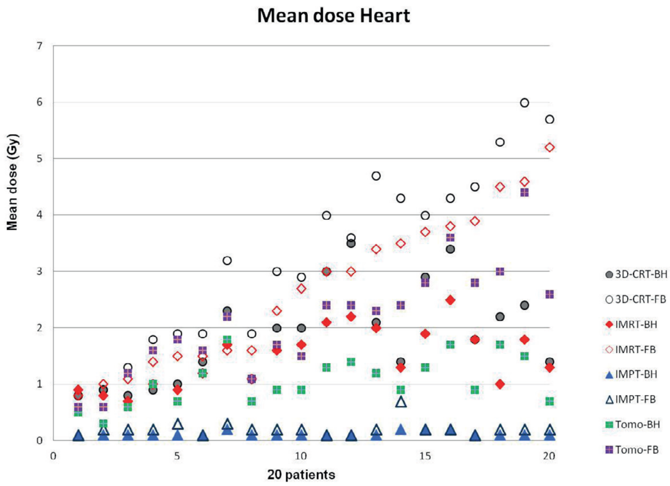

Figure 2. The various treatment planning techniques, with and without breath-hold. The 20 cases were rearranged using the increasing (from left to right) IMRT FB technique values.

A mean deep inspiration breath-hold of 75% of the maximum aspiratory capacity of the patient needs to be achieved to attain the largest thoracic amplitude. With a shallow breath-hold without increasing this amplitude the heart still may receive a relatively high radiation dose. The ABC method informs the staff with vital information about the maximal amplitude of each individual patient.

A breath-hold technique can also be used to reduce the dose in the ipsilateral lung. This is valid for patients with right-sided breast cancer radiotherapy as well. In all patients decreasing the risk of developing a secondary lung cancer is of importance and, therefore, the dose in the lungs should be kept as low as possible, which specifically applies to smokers [45].

Finally, when combining a breath-hold technique with a tangential IMRT technique a further dose reduction was found, especially in the caudal part of the treatment fields. Therefore, nowadays we advise to use a tangential IMRT technique in combination with a breath-hold technique. To note: the Active Breathing Control technique has the advantage of taking into account the thoracic amplitude. Whether the CTV-PTV margins can be decreased, with the use of a breath-hold technique, needs to be examined in future studies.

Coronary artery disease and breast cancer radiotherapy
Several pre-clinical studies reported that arteries are particularly sensitive to radiation [73-75]. It appeared that the carotid intima-media thickness increased linearly with increasing length of time after radiotherapy [76]. Stewart recently suggested that microvascular changes and atherosclerosis in experimental studies are the likely underlying causes of radiation-induced cardiovascular damage, at ≥ 2Gy and ≥ 8Gy, respectively, to the whole heart or a part of the heart [77,78].
Whetal et al. confirmed that the presence of radiation-induced calcium deposits is considered as a surrogate marker for radiation-induced atherosclerotic lesions in patients treated for Hodgkin's lymphoma [79]. Also Daniels et al. found a high prevalence of asymptomatic coronary artery disease. They stated that this might justify the screening of Hodgkin disease survivors who had received mediastinal radiotherapy. However, they performed a computed tomographic coronary angiography, which is an invasive method [80].

Gondrie et al. tried to incorporate unexpected image findings, such as arterial calcium scores, and outcome data relevant to patients. They state that truly meaningful conclusions about the prognostic value of unexpected and emerging image findings can be reached and used to improve patient-care [81]. Jairam et al. presented in 2014 a calculation tool, which can be used in daily practice by radiologists to determine whether a subject has high calcifications scores relative to other patients with the same age and gender [82].

Groarke et al. claimed that a low threshold for screening with non-invasive imaging might help to identify injury at a stage where timely intervention may reduce cardiovascular morbidity and mortality in cancer survivors. But much cheaper and easier would be to use the low dose planning CT scan used for radiation treatment planning [83] together with the calculation tool of Jairam et al. [82].

Future perspective: coronary artery disease
The calculation tool of Jairam et al. [82] could be applied to identify patients with a high rate of calcifications on the CT scan and, therefore, having a high risk of developing a coronary vascular event. These patients could be proposed for a radiation technique with a low dose in the heart and the coronary arteries: e.g. the proton technique or if applicable an APBI technique.

Position verification in breast cancer radiotherapy
Another crucial step in the radiation treatment process is the position verification procedure on the linear accelerator. Several studies aimed at improving this process in order to achieve daily optimal patient positioning. It appeared that an on-line clip match procedure improves the localisation of the treatment volume [84-88]. In our institution we studied the optimal position verification procedure since 2008 [89]. In 2014 we started with an on-line surgical tantalum clips match as a position verification procedure for the boost fields [90].

Future perspective: position verification
To reduce the risk of geographical miss an on-line position procedure is of fundamental importance in administering a boost or external APBI. Instead of aiming at the bony structures we aim directly at the lumpectomy cavity by matching on the tantalum clips that represent the lumpectomy cavity. Tantalum clips are widely available and less expensive compared to gold markers. These clips can be placed in the lumpectomy cavity on a routinely basis. It is, therefore, easy to incorporate this procedure into daily practice.

Concluding remarks

As was stated before, lessons can be learned from the various published studies. Improvements in radiation techniques have been achieved. However, the surrounding healthy tissue will still receive a radiation dose, when the glandular breast tissue is irradiated after breast conserving surgery. Only omitting radiation treatment completely will prevent this. Up until now no subgroup of patients can be defined in whom radiotherapy can be safely omitted, since the risk on ipsilateral recurrence is significantly reduced when applying radiotherapy. However, in selected subgroups, for example in patients older than 70 years, with low-grade, small ductal carcinoma in situ [91], omitting radiation therapy after complete excision of the tumour and perform a wait and see policy could be an option.

In future, we need to focus on individualisation of the radiation treatment, taking into account tumour and patient-related risk factors, to try to cure the patient with the optimal and most convenient type of treatment, and reduce the treatment-related consequences as much as possible. In order to achieve the most optimal treatment we need to aim at an optimal definition of target volumes. Furthermore, several radiation treatment techniques could be used to reduce the dose in the heart and the LAD: i.e. tangential IMRT in combination with breath-hold, external APBI, IORT or, in specific cases by using protons. And, as a last step in the radiation treatment process, performing an optimal procedure to correct for positioning inaccuracies is a prerequisite. Thereby, preserving the patient's quality of life is of utmost importance. Finally, this needs to be tailored according to the patient's preferences, by means of a process of shared decision making.

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