Modern radiotherapy techniques for breast cancer

Authors K. Erven, C. Weltens, E. Van Limbergen, W. Van den Bogaert

Key words Breast cancer, radiotherapy, treatment technique

Summary

The efficacy of radiotherapy (RT) in reducing breast cancer (BC) mortality is well established. Currently, the challenge is to minimize normal tissue complications, improve cosmetic outcome and reduce the overall treatment time without losing treatment efficacy. Technological advances allowed the development of new RT techniques, that are able to improve the radiation dose distribution and dose delivery in BC patients. The following approaches will be discussed: three dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), respiratory gated RT, prone positioning, accelerated partial breast RT (APBI) and image-guided RT (IGRT).

(BJMO 2008;Vol 2;6:308-14)

Introduction

For many years, mastectomy was the standard treatment to achieve local control in BC. Breast-conserving therapy (BCT) was developed in the seventies and resulted in an equivalent survival in several phase III trials.[1-2] A meta-analysis of the *Early BC Trialists Collaborative Group (EBCTCG)* revealed the need for RT after breast conserving surgery by showing that breast irradiation reduced the 5-year local recurrence rate from 26% to 7% and the 15-year risk of BC mortality from 35.9 % to 30.5%. Similar proportional reductions in local recurrence rate (23% to 6%) and BC mortality (60.1% to 54.7%) were demonstrated for node-positive disease after postmastectomy RT to the chest wall and regional (internal mammary, supraclavicular and axillary) lymph nodes.[3]

The clinical benefit of RT in the treatment of BC must be balanced against the documented risk for early and late side-effects, including predominantly skin, pulmonary and cardiac toxicity. Nowadays, the risk for cardiac toxicity is amplified by the widespread and growing use of adjuvant systemic chemotherapy and targeted therapies. However, most data on radiation-induced damage after long latency periods (15-20 years) come from old series that applied obsolete RT techniques. Contemporary treatment seems to be less harmful, although long-term data are not yet available.[4]

Over the last decade, new developments in computer technology have led to an enormous evolution in RT techniques. Together with an extensive implementation of imaging modalities in the RT practice, these new techniques allow a more accurate delivery of the radiation dose.

Standard two-dimensional RT (2D-RT)

Standard radiation therapy consists of 50 Gy in daily fractions of 2 Gy to the whole breast and a boost to the tumourbed of 10-16 Gy. Patients are traditionally installed in supine position on an angled breast board with one or both arms stretched above the head.

A standard field set-up is used, with tangential fields covering the breast and field edges based on surface anatomy. For treatment planning, only a limited amount of contours of the patients outline are available. Standard fields and 2D planning can only partly account for individual variations in patient anatomy.

Dose distributions with the standard technique are acceptable in most patients. However, when the target volume becomes more complex, aberrations

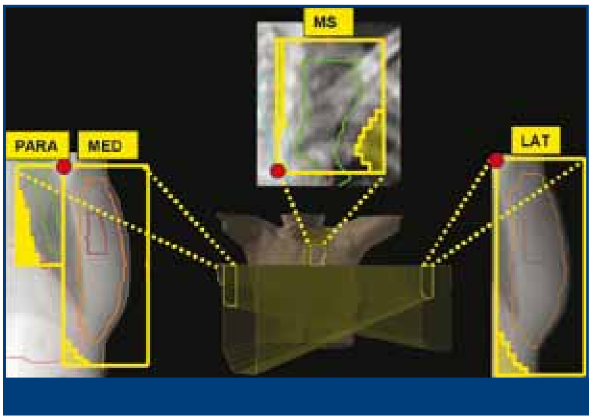

Figure 1. Example of a 4 field 3D-CRT technique, using quarter beams and a single isocenter (red dot).
LAT= lateral tangential breast field, MED= medial tangential breast field, PARA= parasternal oblique field, MS= median subclavia anterior field

in dose homogeneity occur that may contribute to clinically significant toxicity. Particularly in patients with large breasts, the variation in thickness across the target volume results in the inability to deliver a homogeneous dose throughout the breast. Wedges are used for missing tissue compensation, but can only adjust for dose heterogeneity in a 2-dimensional plane. Furthermore, the inclusion of the locoregional lymph nodes in the target volume makes treatment planning more difficult. To cover this complex target volume in close proximity to the heart and the lungs, different fields have to be aligned. The dose distribution near the junction area of the fields is often not homogeneous.[5]

Three-dimensional conformal RT (3D-CRT)

New developments in computer technology allowed the integration of CT-information in the RT planning system, enabling the design of radiation beams that are based on patient-specific 3D anatomical information. A modern linear accelerator with a multileaf collimator (MLC) can deliver these conformal beams to the patient.
In general, there is a large variability in the curvature of the chest wall, the separation of the heart from the breast target and the location of the glandular breast tissue and regional lymph nodes.[6] Therefore, individualisation of treatment planning and delivery results in a more optimal dose distribution.
In breast only irradiation, the 3D alignment of the tangential beams allows improved coverage of the breast tissue and reduction of the volume of irradiated heart and lung tissue.[7] In locoregional breast irradiation however, several 3D techniques have been described to solve the problems of inhomogeneous dose distribution that occur frequently at the matchlines between the tangential breast fields and anterior or oblique lymph node fields. A perfect match can be obtained by half or quarter beams that can easily be delivered with a modern linear accelerator, enabling asymmetric collimation in 2 directions (*Figure 1*). Using full CT-data, the location of the matchline between the different fields can be customized, depending on the patients' anatomy (e.g. subclavicular matchline between anterior supraclavicular field and tangential breast fields at the level where the internal mammary / medial supraclavicular nodal chain moves from its caudal more superficial to its cranial more deep location). Some techniques use separate anterior or oblique fields to cover the internal mammary lymph node chain, other techniques include those lymph nodes in the tangential breast fields. Comparisons between different locoregional 3D techniques show that every technique has some advantages but none of them can combine the best target coverage with the maximal sparing of critical structures in all patients. The decision which technique to use should be patient-specific, considering tumour, patient and treatment related characteristics.[8] For some, mostly larger patients, no acceptable technique can be found; these patients are more likely to benefit from advanced techniques such as intensity-modulated RT.

Intensity-modulated RT (IMRT)

IMRT is a treatment technique that allows modulation of the beam intensity within the treatment fields to obtain highly conformal dose delivery. Several techniques for IMRT in BC have been developed, varying from fairly simple conventional tangents to complex set-ups with multiple fields.
For the irradiation of the breast alone, all these techniques improved dose uniformity and reduced doses to the heart and lung.[8,9] Since the multi-field solutions often suffer from increased low doses to the surrounding normal tissues, most investigators propose a technique using two conventional tangential fields. A large amount of the dose is given by parallel opposed open beams; a part of the dose is given by several MLC shaped segments, each delivering a small amount of monitor units.[10] These segments are generated to compensate for missing tissue and block organs at risk. Whether the demonstrated improve-

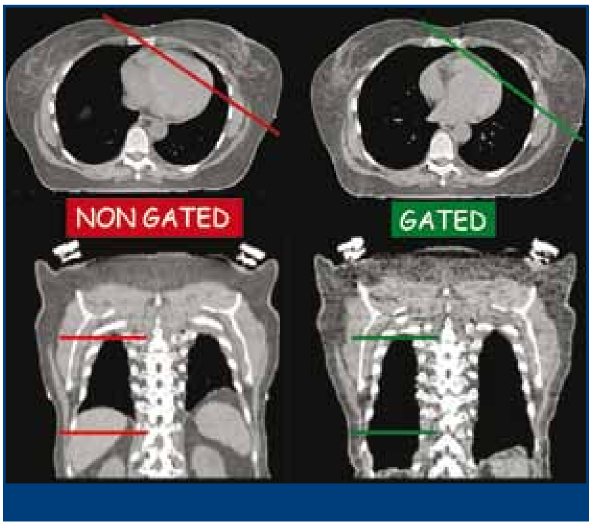

Figure 2. Transversal and frontal slices of a non gated and a deep inspiration gated CT. The posterior field edges of the tangential breast fields are indicated on the transverse slices and the cranial and caudal field edges on the frontal slices. Note the posterior movement of the heart in inspiration (out of the field) and the increase in total lung volume, reflecting the decrease in lung density.

ments in dosimetric performance translate into a clinical benefit was tested in two randomised trials. One included 358 patients and showed a significant reduction in the amount of patients experiencing moist desquamation up to 6 weeks after treatment (31.2% with IMRT, compared to 47.8% with standard 2D treatment).[8] In the other phase III trial, photographic assessment was done up to 5 years after treatment to evaluate the change in breast size and shape. A statistically significant improvement in the breast appearance was seen in patients treated with IMRT compared to standard 2D treatment.[9]

The application of IMRT in the treatment of locoregional BC is more challenging. Due to the complex target volume, more advanced IMRT techniques are proposed, using multiple beams and inverse planning. There is no agreement in the orientation and amount of beams amongst the different planning studies. Up to 11 beams, covering an arc of 180° to 360° are advocated. In general, all techniques were able to improve the dose distributions, compared to non-intensity modulated 3D-CRT plans. Some IMRT techniques are good at sparing one structure, whereas others are better at sparing other structures. Depending on the technique used, increased doses to the contralateral breast, contralateral lung, oesophagus, thyroid and humeral head are reported. The optimal geometric beam arrangement is determined by the anatomy of the patient, the location of the target structures and the desire to minimize radiation dose to healthy tissues. Therefore, the choice of the best technique must be patient-specific.[11,12]

Due to the use of sharp dose gradients in IMRT, the effects of patient set-up errors and breathing motion on the dose distributions are more important and must be taken into account, when evaluating the potential gains of IMRT over 3D-CRT. Furthermore, the benefits of IMRT must be weighted against the increase in overall low radiation dose. In multiple beam IMRT, more monitor units are needed to deliver the desired dose. This results in more leakage radiation and a higher total-body dose. The carcinogenic risk after IMRT is estimated to be almost doubled compared to non-intensity modulated 3D treatment.[13] This is especially relevant for BC patients as they have a long life-expectancy.

The clinical relevance of the benefits and drawbacks of intensity modulated locoregional breast RT is yet to be determined. Currently, no clinical data are available on the use of IMRT in locoregional breast RT.

Respiratory gating

In respiratory gating, the radiation treatment is synchronized with the patients' individual breathing pattern. The radiation beam is turned on only during a pre-specified phase of the respiratory cycle, thereby modifying the relative position of the target structures and normal organs in the radiation field. It has been demonstrated that gating for breast irradiation is most favourably done in inspiration. In this respiratory phase, the distance between the breast and the heart is enlarged and the lung density is reduced (*Figure 2*).[14-16]

To perform a gated treatment, dedicated devices are available that can record the patients' breathing pattern, allow for coaching of the patients to achieve the desired breathing pattern (deep inspiration breath hold or deeply free breathing) and gate the CT-scan and treatment machine in the desired phase of the respiratory cycle.

Large dosimetric benefits of respiratory gating, using a moderate deep inspiration breath hold (mDIBH) technique for treatment of the breast and the internal mammary nodes, treated by means of wide tangential fields with IMRT compensation are reported. The volume of both lungs receiving 20 Gy (V_{20}) reduced from 20.4% for normal breathing (NB) to 15.7% for mDIBH. For the left-sided patients, the volume of heart receiving 30 Gy (V_{30}) was reduced

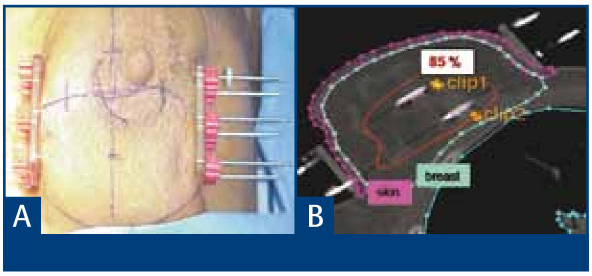

Figure 3. Multicatheter interstitial brachytherapy. A: External appearance of the implant. B: Transversal CT-slice with indication of the 85% isodose (–), at large distance from the skin.

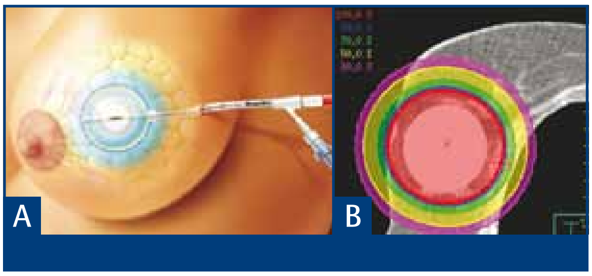

Figure 4. Intracavitary balloon brachytherapy. A: Presentation of the Mammosite® catheter. B: Transversal CT-slice with indication of the isodoses (view color code). Note the 100% isodose reaching the skin.

from 16.3% (NB) to 3.1% (mDIBH).[15] Because of possible problems of reproducibility and patient cooperation in case of breath hold procedures, others evaluated a free breathing technique. Significant differences in heart and lung doses were obtained when treatment plans based on a CT-scan gated in the end expiration phase (EG) were compared with the ones gated in the end inspiration phase (IG). The volume of heart receiving 24 Gy (V_{24}) reduced from 19.2% (EG) to 2.8 % (IG) and the volume of ipsilateral lung, receiving 24 Gy (V_{24}) from 45.6% (EG) to 29.5% (IG).[16] To date, no reports on clinical outcome after gated breast treatment are available.

Accelerated Partial Breast Irradiation (APBI)

It has been shown that about 85% of local recurrences after breast conserving surgery and whole breast irradiation (WBI) occur in close proximity to the original tumour bed.[17] Therefore, irradiation of the whole breast may not be necessary in all cases of early-stage BC. This has led to the development of partial breast irradiation (PBI), a technique designed to treat only the tissue surrounding the tumourectomy cavity. A reduction in treatment volume allows for the delivery of larger treatment fractions in a shorter time period. In accelerated partial breast irradiation (APBI) the treatment time is reduced to 1-10 days. Careful patient selection criteria must be applied when APBI is considered. The eligibility criteria are still under investigation and often differ between different studies, but in general the following criteria for low risk of recurrence are considered: unifocal and unicentric disease, tumour size ≤ 3 cm, tumour-free resection margin ≥ 2mm, no axillary lymph node involvement and patient age > 40 years. A variety of treatment techniques are developed to deliver APBI. Currently, the most commonly used methods are interstitial multicatheter brachytherapy, intracavitary balloon brachytherapy, intraoperative RT, and 3D conformal external photon beam RT.[18]
Currently there is enough data to demonstrate the safety and effectiveness of APBI in a carefully selected subgroup with favourable disease characteristics.[18] Longer follow-up and randomised trials are needed to conclusively assess the potential of APBI. Phase III trials are ongoing for each APBI technique. In the absence of randomised evidence of the equivalence between WBI and APBI, routine use of APBI, outside clinical trials is discouraged.[19]

Interstitial multicatheter brachytherapy

This technique requires the highest level of skill but also offers the most flexible and adaptable approach. Multiple catheters are placed in the breast tissue surrounding the tumourectomy cavity at 1 to 2 cm intervals (*Figure 3*). Interstitial brachytherapy can be administered with either a low-dose rate (LDR), a pulsed dose rate (PDR) or a high-dose rate (HDR) technique. Common dose delivery regimens for LDR and PDR are 45 to 50 Gy in 3 to 6 days and for HDR 32-34 Gy in 8-10 twice-daily fractions.[19]

Intracavitary balloon brachytherapy

This approach represents a simplification of multicatheter brachytherapy techniques. It relies on the placement of a radioactive source within a balloon catheter device (Mammosite®) that fits inside the tumourectomy cavity and treats 1 cm of tissue surrounding the cavity (*Figure 4*). MammoSite® employs only high-dose rate (HDR) regimens, with a typical fractionation of 34 Gy in 10 fractions, twice daily.
The major drawback to the use of this technique is standard spherical dose distribution that can result

Figure 5. On-board imager (OBI, Varian®). X-ray tube and kV-flat panel imager mounted on the gantry of the linear accelerator, orthogonal to the MV source.

in an overdosage to the skin. Therefore, it is mandatory to have a skin source distance of at least 10 to 15 mm.[19] This limits the indication to deep seated central tumoural cavities in large breasts.

Intra-operative RT (IORT)

In IORT a single fractional dose (+/- 20 Gy), targeted at the tumour bed, is delivered during surgery, using electrons or low energetic X-rays.[18]

A major advantage of this approach is the complete skin sparing and the possibility to avoid the exposure of the underlying lungs and heart by shielding the thoracic wall with a lead plate. A disadvantage is that radiation is completed before the final pathology report is known and that this information cannot be incorporated in the patient selection criteria.

External beam 3D-CRT

3D-CRT with and without intensity modulation, has been used to develop an external beam technique to treat the tumourectomy cavity. Multiple beams are used to deliver 34 to 38 Gy in 10 twice-daily fractions.

Advantages of 3D-CRT/IMRT over the other APBI approaches include the non-invasiveness and the improved dose homogeneity with potential reduction in normal breast tissue toxicity. On the other hand, target volume definition and localisation can be more difficult.

Prone positioning

Recent clinical reports suggest that prone positioning of patients during breast radiation may allow for better sparing of normal organs, particularly in patients with large or pendulous breasts.[20-22] Dedicated breast boards are developed to establish a stable prone patient position with the breast hanging free from the thoracic wall, away from the underlying organs. In general, dose homogeneity is improved by the prone technique. However, target coverage at the medial and lateral borders of the breast close to chest wall may be impaired, due to the more limited accessibility for treatment beams in this position. In all studies, lung doses could significantly be reduced, whereas the sparing effect on the heart was less clear, because of anterior displacement of the heart in this position.[21] Furthermore the risk of epidermolysis is reduced, because of the elimination of skin folds. The effect of this position on the application of planning target volume (PTV) margins (margins that account for possible uncertainties in patient positioning, organ motion, organ deformation, etc.) around the clinical target volume (CTV) for treatment planning is two-fold. On the one hand, breathing motion is less pronounced, so intra-fraction motion is smaller. On the other hand, patient set-up variations can be significantly larger, leading to an increased inter-fraction variation.

This technique was first described by a group from the *Memorial Sloan-Kettering Centre (MSKC)*. They recently reported their 5-year follow-up data in 245 patients, showing a similar disease control with a favourable toxicity profile, compared to a historical control group. Prone-WBI has become the preferred method of therapy for patients requiring breast-only radiation in that centre.[22]

Image-guided RT (IGRT)

IGRT is used to measure and correct positional errors of radiation fields immediately prior and during treatment delivery. Currently, linear accelerators can be equipped with various imaging modalities, that allow the acquisition of anatomical images of the patient in treatment position. For the radiation source, one can either employ the megavoltage (MV) treatment beam or a kilovoltage (kV) X-ray source that is mounted on the linear accelerator and can provide 2D or 3D (cone beam CT) images (*Figure 5*). The advantage of kV imaging is the improved soft-tissue contrast and better visualisation of surgical clips. Clip-based image guidance is a useful tool for the set-up of patients treated with external beam

Key messages for clinical practice

1. The large interpatient variability in the location of the regional lymph nodes supports the use of CT-planning for locoregional breast irradiation to improve target coverage and homogeneity.
2. Each 3D technique (+/- intensity modulation) for locoregional breast irradiation has its own drawbacks and advantages. The decision which technique to use should be patient-specific, considering tumour, patient and treatment related characteristics.
3. For breast only treatment, simple IMRT with tangential fields and MLC shaped segments is an effective way to improve dose homogeneity, particularly in patients with large breasts.
4. For locoregional treatment, multifield IMRT solutions are proposed. They can give rise to an increase in overall low radiation dose and consequently in carcinogenic risk. The clinical relevance of these techniques is yet to be determined.
5. Respiratory gated RT in deep inspiration is a powerful tool to reduce cardiac toxicity in left-sided BC patients.
6. APBI appears to be a safe and effective treatment in a carefully selected subgroup with favourable disease characteristics. However, its routine use is discouraged, as long as no long-term, randomised data are available.
7. Radiation in prone position is a good option to reduce skin and lung toxicity in patients with pendulous breasts.
8. The implementation of IGRT should join the implementation of new techniques to assure an accurate treatment delivery.

APBI. It compared favourably with traditional bony alignment and may allow smaller PTV margins.[23]

Conclusion

New breast irradiation techniques (IMRT, respiratory gating, APBI and prone positioning) were described that are able to provide more conformal and homogeneous dose distributions. However, these dosimetrical benefits can only be translated into a clinical benefit if the treatment plan is accurately delivered. This is even more important in highly conformal plans that are intrinsically more vulnerable to geographical misses, especially when the treatment is delivered in a hypofractionated manner. Therefore, the implementation of IGRT should go along with the implementation of new techniques to assure an accurate treatment delivery. Furthermore, long-term clinical outcome data should be awaited before the routine implementation of these new techniques.

References

1. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early BC. N Engl J Med 2002;347:1227-32.

2. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive BC. N Engl J Med 2002;347:1233-41.

3. Early BC Trialists' Collaborative Group (EBCTCG). Effects of RT and of differences in the extent of surgery for early BC on local recurrence and 15-year survival. Lancet 2005;366:2087-106.

4. Van de Steene J, Vinh-Hung V, Cutuli B and Storme G.

Adjuvnat RT for BC: effects of longer follow-up. Radiother. Oncol. 2004;72:35-43.
5. Erven K and Van Limbergen E. Regional lymph node irradiation in BC. Future Oncology 2007;3:343-352.
6. Bentel G, Marks LB, Hardenberg P and Prosnitz L. Variability of the location of internal mammary vessels and glandular breast tissue in BC patients undergoing routine CT-based treatment planning. Int J Radiat Oncol Biol Phys 1999;44:1017-25.
7. Hurkmans CW, Cho BC, Damen E, Zijp L and Mijnheer BJ. Reduction of cardiac and lung complication probabilities after breast irradiation using conformal RT with or without intensity modulation. Radiother Oncol 2002;62:163-71.
8. Pignol JP, Olivotto I, Rakovitch E and Paszat L. A multicenter radomized trial of breast intensity-modulated radiation therapy to reduce acute dermatitis. J Clin Oncol 2008; 26:2085-92.
9. Donovan E, Bleakley N, Denhom E and Evans P. Randomised trial of standard 3D RT versus intensity modulated RT in patients prescribed breast RT. Radiother. Oncol. 2007;82:254-64.
10. Van Limbergen E, Weltens C. New trends in RT for BC Curr Opin Oncol 2006;18:555-62.
11. Dogan N, Cuittino L, Lloyd R, Bump EA and Arthur DW. Optimized dose coverage of regional lymph nodes in BC: the role of intensity-modulated RT. Int J Radiat Oncol Biol Phys 2007;68:1238-50.
12. Beckham WA, Popescu CC, Patenaude VV, Wai ES and Olivotto IA. Is multibeam IMRT better than standard treatment for patients with left-sided BC. Int J Radiat Oncol Biol Phys 2007;69:918-24.
13. Hall EJ and Phil D. IMRT, protons, and the risk of secondary cancer. Int J Radiat Oncol Biol Phys 2006;65:1-7.
14. Sixel K. Aznar M. and Ung Y. Deep inspiration breath hold to reduce irradiated heart volume in BC patients. Int J Radiat Oncol Biol Phys 2001;49:199-204.
15. Remouchamps VM, Vicini FA, Sharpe MB, Kestin LL, Martinez AA, Wong JW. Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. Int J Radiat Oncol Biol Phys 2003;55:392-406.
16. Korreman SS, Pedersen AN, Jakobi Nottrup T, Specht L and Nyström H. Breathing adapted RT for BC: Comparison of free breathing gating with the breath-hold technique. Radiother Oncol 2005;76:311-18.
17. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P et al. RT after breast-conserving surgery in small breast carcinoma: long-term results of a randomised trial. Ann Oncol 2001;12:997-1003.
18. Orecchia R and Fossati P. Partial breast irradiation: ready for routine? The breast 2007:16;S89-97.
19. Sauer R, Sautter-Bihl M-L, Budach W, Feyer P, Harms W, Souchan R, et al. Accelerated partial breast irradiation. Consensus statement of 3 German oncology societies. Cancer 2007;110:1187-1194.
20. Buijsen J, Jager J, Bovendeerd J, Voncken R, Borger J, Boersma L et al. Prone breast irradiation for pendulous breasts. Radiother Oncol 2007;82:337-40.
21. Chino J and Marks L. Prone positioning causes the heart to be displaced anteriorly within the thorax: implications for BC treatment. Int J Radiat Oncol Biol Phys 2007;69:1124-30.
22. Stegman LD, Beal KP, Hunt MA, Fornier MN and McCormick B. Long-term clinical outcomes of whole-breast irradiation delivered in the prone position. Int J Radiat Oncol Biol Phys 2007;68:73-81.
23. Hasan Y, Kom L, Mus A, Martinez A, Vicini F and Yan D. Image guidance in external beam accelerated partial breast irradiation: comparison of surrogates for the lumpectomy cavity. Int J Radiat Oncol Biol Phys 2008;70:619-25.

Correspondence address

Author: K. Erven, C. Weltens, E. Van Limbergen, W. Van den Bogaert
Department of Radiation Oncology, University Hospital Gasthuisberg, Leuven, Belgium

Please send all correspondence to:
Dr. K. Erven
Department of Radiation Oncology
University Hospital Gasthuisberg
Herestraat 49
3000 Leuven
Belgium
Tel: 0032 (0)16 347600
Fax: 0032 (0)16 347623
Katrien.Erven@uzleuven.be

Conflicts of interest: the authors have nothing to disclose and indicate no potential conflicts of interest.