



Original Article

Injection of radiopaque hydrogel at time of lumpectomy improves the target definition for adjuvant radiotherapy



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ARTICLE INFO

Article history:

Received 28 June 2018

Received in revised form 14 October 2018

Accepted 4 November 2018

Available online 17 December 2018

Keywords:

Breast radiotherapy
Oncoplastic surgery
Seroma segmentation
Opaque hydrogel

ABSTRACT

Background and purpose: During oncoplastic breast-conserving surgery (BCS), the surgical cavity is closed to reduce seroma formation. This makes the radiotherapy target definition using clips challenging, leading to poor inter-observer agreement and potentially geographical misses. We hypothesize that injecting a radiopaque hydrogel in the lumpectomy cavity before closure improves radiotherapy target definition and agreement between observers.

Materials and methods: Women undergoing BCS in a single university hospital were prospectively accrued in the study. Three to 9 ml of iodinated PolyEthylene Glycol (PEG) hydrogel and clips were inserted in the lumpectomy cavity. A CT-scan was performed at 4 to 6 weeks. CT images of BCS patients with standard clips only were used as control group, matched on age, specimen weight, and distance between clips. Six radiation oncologists delineated the tumor bed volumes and rated the cavity visualization scores (CVS). The primary endpoint was the agreement between observers measured using a Conformity Index (Cx). **Results:** Forty-two patients were included, 21 hydrogel procedures and 21 controls, resulting in 315 observer pairs. The feasibility of the intervention was 100%. The median Cx was higher in the intervention group (Cx = 0.70, IQR [0.54–0.79]) than in the control group (Cx = 0.54, IQR [0.42–0.66]), $p < 0.00$, as were the CVS (3.5 [2.5–4.5] versus 2.5 [2–3.5], $p < 0.001$). The rate of surgical site infections was similar to literature.

Conclusions: The use of radiopaque PEG enables to identify the lumpectomy cavity, resulting in a high inter-observer agreement for radiotherapy target definition. This intervention is easy to perform and blend well into current practice.

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For localized cancers, breast-conserving therapy (BCT), including limited surgery and adjuvant whole breast radiotherapy, is equivalent to mastectomy in regard to oncologic outcomes while enabling breast preservation [1]. Oncoplastic techniques have been increasingly used worldwide to improve cosmesis [2–4]. Those techniques involve, at minimum, a simple volume displacement (level 1 oncoplastic technique), as the breast parenchyma is approximated to close the lumpectomy cavity [5]. In so doing, the seroma is limited in size, and it often becomes invisible on a CT-scan. Eventually this technique creates challenges for tumor bed delineation at the time of adjuvant radiotherapy planning [6]. Accurate tumor bed delineation to target breast radiotherapy

is particularly critical for accelerated partial breast irradiation (APBI) or when a boost dose is required. During APBI, only the part of the breast immediately surrounding the tumor bed is irradiated [7–11]. Also, young or high-risk patients are benefiting from a boost dose to the tumor bed after or during whole breast radiotherapy [12].

Inaccurate target definition carries the risk of a radiation geographical miss, which, in turn, might lead to an increased risk of local recurrence, especially for APBI. Furthermore, if the tumor bed delineation is enlarged due to uncertainties, there is an increased risk of toxicity [13–15]. Finally, if the target cannot be appropriately defined, some patients may be declined for patient-friendly APBI techniques [15–19]. Traditionally, surgical clips are placed at the time of surgery to guide the tumor bed delineation. However, a recent study by den Hartogh shows that radiotherapy target definition using clips has poor inter-observer

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agreement in patients following oncoplastic surgery [6]. Thus, the attempt to improve surgical outcome by performing oncoplastic techniques might impair radiotherapy treatment outcomes.

A recent development in radiation oncology is the use of temporary injectable hydrogels. Among others, polyethylene glycol (PEG) radiopaque hydrogel is successfully used as a spacer to remove critical structures from the high dose area, such as the rectum in prostate radiotherapy [20]. Also, iodinated PEG hydrogel has been proposed as a tissue marker [21].

Ciernik et al. tested a PEG hydrogel marker to visualize the cavity after lumpectomy and suggested a high level of inter-observer agreement for target delineation [22]. The marker contains PEG with less than 1% iodine, and this material has a high imaging contrast on CT, MRI and, to a lesser extent, on ultrasound up to 3 months. Reabsorption and clearance takes place approximately 7 months after implantation.

We report a prospective clinical cohort study testing the radiopaque hydrogel to improve radiotherapy target definition following oncoplastic breast conserving surgery. Our aim was to assess if the injection in the lumpectomy cavity before closure was safe, feasible, and increased inter-observer agreement for the radiotherapy target definition.

Patients and methods

Study population

The study design was a prospective intervention cohort study with a matched control group. The study was approved by the Erasmus MC research ethic board and registered at the Netherlands Trial Register (NTR-6610).

Eligible patients included women with a diagnosis of breast cancer or DCIS planned for breast-conserving surgery, with full-thickness closure corresponding to level 1 oncoplastic breast surgery, and adjuvant radiotherapy. Patients with oncoplastic surgery of level 2 or more (volume replacement), pre-operative indication for adjuvant chemotherapy, or an allergy for PEG or iodine were excluded. Selected patients were included after written informed consent was obtained.

Treatments

Surgical procedures were performed in a large secondary teaching hospital in Rotterdam, the Netherlands (Franciscus Gasthuis and Vlietland). After tumor resection and hemostasis were achieved, five surgical clips were placed, according to standard protocol, to define the cavity walls: including one positioned deep toward the fascia pectoralis and four in each radial direction [23]. Subsequently, any undermining of the fibroglandular tissue from the pectoralis muscle and/or skin was performed. Then, 3 to 9 ml of radiopaque PEG hydrogel (TraceIT[®], Augmenix Inc, Bedford, MA) was instilled in the cavity and coated onto the tumor cavity walls with the fingertips. The cavity was closed following oncoplastic protocol with the suture of at least one deep, glandular, layer and closure of the most superficial layer and the skin. The amount of product used was recorded and ease of use scored using the System Usability Scale (SUS) [24]. This 10 questions 5-point scale is a simple and reliable tool to measure usability of new technology or products and is widely used in medical research [25]. After referral to radiation oncology, a standard CT-simulation for radiotherapy planning purpose was acquired with images of 2.5 mm thickness and a resolution of $1 \times 1 \text{ mm}^2$ at 120 kilovolt-peak (kVp). The surgical scar and the glandular tissue were marked on the skin with a CT compatible wire.

Patients treated with the hydrogel were matched 1:1 with a cohort of patients treated by the same team of surgeons also per-

forming a level 1 oncoplastic surgery with placement of five surgical clips [23], but without instillation of the hydrogel. Matching was performed on factors known to influence interobserver variability of target definition and/or cavity visibility, ensuring similar resected specimen weight and maximum distance between clips (as predictors of target volume) [26–29], and age (below or above 70 years) as surrogate for breast composition [29].

Target volume delineation

Anonymized CT image sets of both group of patients were transferred to a MIM Symphony 6.6 imaging station (MIM Software Inc, Cleveland, OH). Six experienced and senior radiation oncologists delineated the target volumes in a random sequence and were blinded to each other's contours, by making the sets of CT-images available to each radiation oncologist separately (Fig. 1). Each patient's pre-operative information and imaging, surgical report and pathology report were available.

For the patients in the intervention group, the radiation oncologists were asked to contour the tumor bed with the following instruction: "Please contour the tumor bed volume as usual, using information of the CT density (including the hydrogel) and the clips". For the control group, the radiation oncologists were asked to delineate using the following instruction: "Please contour the tumor bed volume as usual, using information of the CT density and the clips". Additionally, all six radiation oncologists were asked to rate the cavity visualization score (CVS) [26,30] and record the time needed for contouring per patient. The CVS is a metric assessing the visibility of the lumpectomy cavity on CT on a 5-point scale ranging from "no cavity visible" (CVS 1) to "homogeneous cavity with clearly identified margins" (CVS 5) (Fig. 2), that is frequently used in studies on target definition [6,31].

Analysis

The primary outcome measure was the Conformity Index (Cx), defined by the ratio between the volume of agreement of the defined target volumes divided by the encompassing volume for each observer pair [6]. Secondary outcome measures included the distance between the center of mass of the target volumes (dCOM), the target volumes in cc, the CVS [26,30], the feasibility of hydrogel injection, adverse events, and ease of use.

A sample size of 21 patients times six observers was calculated, leading to 315 observer pairs in both the intervention and control group. Based on an expected SD in Cx of 0.19 [6,32], $\alpha = 0.05$ and $\beta = 0.2$, this sample size would make it possible to detect an effect size of 0.044 of the primary outcome (Cx) with 95% confidence. Even for a subgroup analysis ($\alpha = 0.025$) on $\text{CVS} \leq 3$ with an expected number of $n = 10$ patients in each group the detectable effect size would be 0.068, which was deemed acceptable.

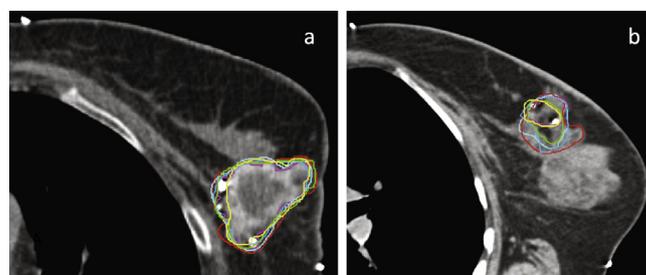


Fig. 1. a/b: Example of tumor bed delineation on CT with (a) and without (b) hydrogel.

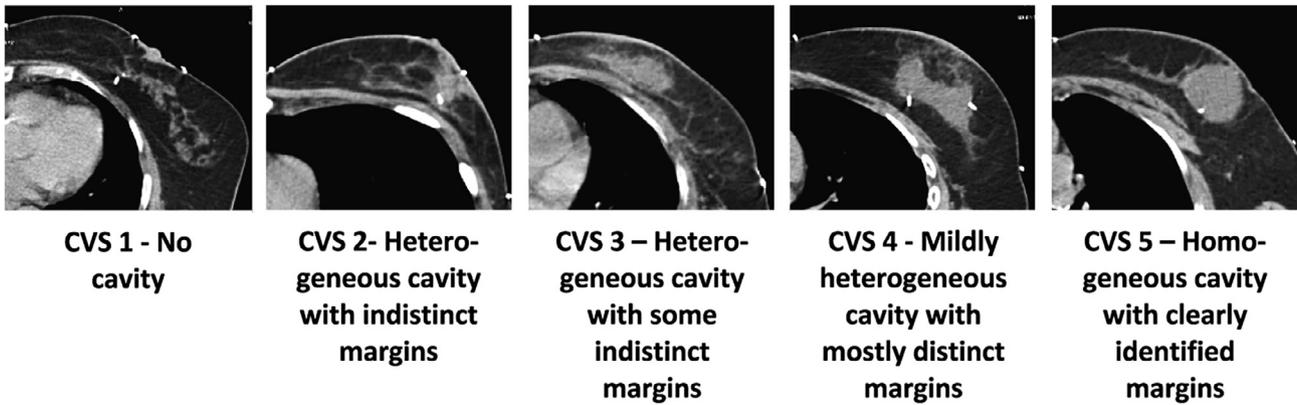


Fig. 2. Cavity Visualization Score description using CT-images of patients included in the control group of the study.

For the primary outcome measure, we reported median values and accompanying interquartile ranges (IQRs) and, as Shapiro-Wilk's normality tests showed this variable was not normally distributed, assessed significance using a Mann-Whitney U-test.

Descriptive statistics were used for the analysis of secondary endpoints, assuming independency of groups. Differences between groups were also assessed using a Mann-Whitney U-test. Multiple linear regression analysis testing the factors influencing the Cx included the following independent variables: group (intervention versus control), mean target volume, CVS per observer pair, and the matching factors as described above. The effect modification was modeled as an interaction effect of group (intervention versus control) times target volume. The feasibility of the hydrogel marker injection and adverse events were described as percentages. IBM SPSS Statistics version 24 was used with two-sided p -values below 0.05 considered statistically significant.

Results

Twenty-four patients were included in the interventional group. Three patients were excluded because they had positive margins on the pathology report and they had a second surgery for re-excision. In these three cases, during re-excision the hydrogel was clearly identifiable, being solid in the surgical cavity and easy to remove. In the control group we randomly matched 21 patients out of 100 possible controls. Patient characteristics are detailed in Table 1. The groups were well balanced in regard to tumor diameter, histology, resected specimen weight, and maximum distance between clips. In the intervention group, patients were 5 years younger, leading to potentially more dense breasts.

The use of hydrogel was technically feasible in all patients. The product was easy to use, with a median SUS score of 100 (IQR [96–100]). Two patients (9.5%) in the intervention group developed a

surgical site infection, and two patients (9.5%) had clinically apparent seroma formation, all being grade 1–2 out of 5 according to the Clavien Dindo classification [33].

Patients in the intervention group had their CT-simulation performed at a median of 39 days post-surgery (IQR [31–46]). For most patients, the hydrogel was easily identified in the surgical cavity on the radiotherapy planning CT. The occurrence of seroma in some cases caused dilution of the hydrogel or, in other cases, formation of a level of hydrogel, not completely filling up the cavity (Fig. 3).

Table 2 summarizes the study findings. The median conformity index was higher in the intervention group, with a Cx of 0.70 (IQR [0.54–0.79]), compared to the control group, with a Cx of 0.54 (IQR [0.42–0.66]), suggesting that the target delineation was less variable in the presence of hydrogel ($p < 0.001$). On the other-hand, contouring in the presence of hydrogel took slightly more time – 5 mn instead of 4 ($p < 0.001$) – and also led to target volumes two and a half times larger being contoured – 26.2 cc instead of 10.2 cc ($p < 0.001$).

Multiple linear regression analysis showed that the adjusted Beta coefficient was 0.09 (95% CI [0.05–0.17]) for group and 0.002 (95% CI [0.001–0.004]) for mean target volume, meaning that both the presence of hydrogel and of a large target volume were significantly associated with a better Cx. Adding the interaction term of intervention times target volume to the model showed that the increase in Cx per unit volume is larger in the presence of gel (adjusted Beta coefficient was 0.005 (95% CI [0.004–0.006]), meaning that with every 2 cc larger volume, the presence of gel, leads to an extra 0.01 increase in Cx. Mean CVS per observer pair was eventually excluded from the model as variable group is positively correlated with a CVS (Spearman's correlation coefficient 0.326, $p < 0.001$). This is logical since the intervention is intended to increase the seroma visibility.

Table 1

Patient characteristics between groups. Data are presented as median values, and inter-quartile ranges within brackets.

	Intervention group (hydrogel + clips) $n = 21$	Control group (clips only) $n = 21$
Age, years	57 [50–64]	62 [50–65]
Microscopic tumor diameter in mm	14.5 [12–18]	15 [9.5–21]
Resected specimen weight in grams	42 [28–66]	45 [35–61]
Histology	19 ductal carcinoma 1 DCIS 1 mucinous carcinoma	15 ductal carcinoma 4 DCIS 1 lobular carcinoma 1 apocrine carcinoma
Laterality	5 Left 16 Right	9 Left 12 Right
Interval between surgery and CT-simulation in days	39 [31–46]	36 [24–55]
Maximum distance between surgical clips on CT in mm	46 [39–52]	45 [31–55]

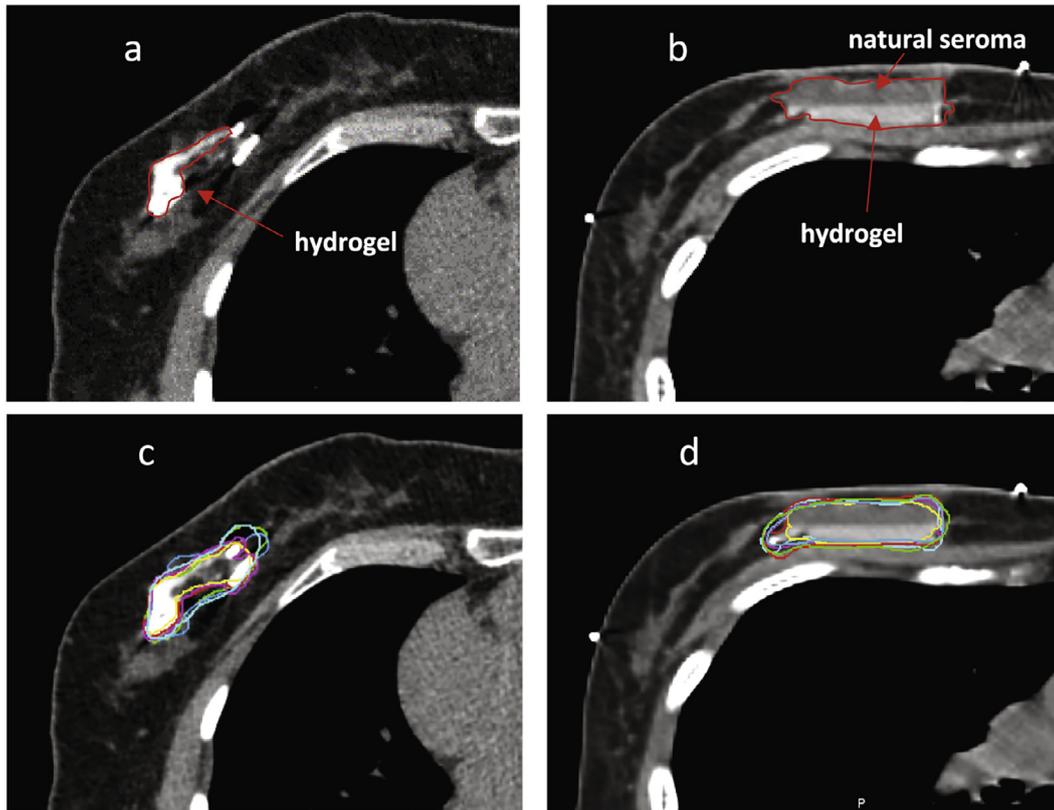


Fig. 3. Example of case without natural seroma (a) and a case with natural seroma (b), showing some dilution and formation of a level of hydrogel, not completely filling up the cavity (shown in red) and the resulting six contours for both cases (c and d). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2

Results for various radiotherapy target delineation metrics. Data are presented as median values with inter-quartile ranges within brackets.

	Intervention group (hydrogel + clips) <i>n</i> = 315**	Control group (clips only) <i>n</i> = 315**	<i>P</i> -value*
Cx	0.70 [0.54–0.79]	0.54 [0.42–0.66]	<0.001
CVS	3.5 [2.5–4.5]	2.5 [2–3.5]	<0.001
dCOM in mm	2.0 [1.1–4.3]	3.1 [1.6–5.3]	<0.001
Target volume in cc	26.2 [15.1–43.8]	10.2 [5.8–22.9]	<0.001
Delineation time in minutes	5 [4–7]	4 [3–5]	<0.001

* Mann–Whitney's U-test.

** *n* = number of observer pairs.

The effect of the intervention was strongest in the matched group of patients with a CVS ≤ 3 in the control group (median Cx 0.67 with hydrogel and clips versus 0.49 with clips alone, $p < 0.001$), meaning in the group of patients where the seroma was difficult to identify, compared to the group of patients with a CVS > 3 in the control group (median Cx 0.74 versus 0.68, $p < 0.001$).

Discussion

This study demonstrates that using a hydrogel loaded with iodine during lumpectomy cavity closure, reduces the variability of target contouring in a population of well trained and highly specialized radiation oncologists.

We report on a simple surgical intervention adding to other solutions to improve radiotherapy target definition for breast

cancer patients, including the use of clips, 3D ultrasound or MR image fusion or simulation. Since inter-observer variability is indicative of the difficulty to accurately define the treatment target volumes among practitioners, those studies examining these options have used the conformity index (Cx) as a measure of accuracy in defining the target volume [28]. Our results compare well with other studies using standardized contouring protocols and surgical clips, which is the current gold standard in radiotherapy [15]. Previous studies evaluating the interobserver agreement for delineation with clips found comparable Cx to the one we reported here for the control group, between 0.56 and 0.61 [27,28,34]. Another study reports a higher agreement using gold fiducial markers, with a Cx of 0.70 [31]. However, none of these studies were performed in a context of a level 1 oncological intervention. A study by Den Hartogh showed that radiotherapy target definition using clips alone for patients with full thickness

closure has a much poorer inter-observer agreement, with a median Cx of 0.44 [6].

The significantly higher Cx in our intervention group than in our control group could be explained by the also significantly higher CVS (3.5 versus 2.5 respectively). The median CVS score of 2.5 (heterogeneous cavity with no to minimal distinct margins) in our control group seems higher than one would have expected. However, a median CVS score of 3 was found in the study by den Hartogh et al. after full thickness closure [6]. This means that full thickness closure not always translates into a loss of cavity. In several cases in our study the full-thickness closure was limited to a single suture, which could be the explanation of the existence of a visible seroma. The higher conformity index found in our intervention group, where all patients had oncological intervention, should be considered as a result supporting the use of hydrogel to improve the quality of the radiation treatment. The intervention group add a larger median target volume compared to the control group (26.2 versus 10.2 cc). However this is not the only explanation why the intervention group had a better Cx, since the regression analysis adjusting for target volume showed that the use of hydrogel was an independent factor of improved Cx. The hydrogel itself accounted for a 9% increase in Cx on average, which is clinically relevant. Interestingly, although the hydrogel itself adds some volume (3 to 9 cc in this study) which may preserve part of the seroma, the median target volume in our intervention group, 26.2 cc, is comparable to the 23 cc found in the study by den Hartogh et al. [6] In cases with relatively large seroma, the visualization was nevertheless facilitated by the presence of radio-opaque gel on the border of the seroma. The effect of the hydrogel use on mean target volumes and consequent planned target volumes (PTVs) could not be assessed in this study.

The hydrogel injection intervention was found feasible, safe and easy to perform. The rate of infection (9.5%) and the formation of a clinically apparent seroma (9.5%) after injection of hydrogel was comparable to the literature for breast-conserving surgery [35–38].

A higher Cx results in a lower risk of geographical miss of the administered radiotherapy, which, in turn, may result in a better outcome in terms of local control. Additionally, with less inter-observer variability, smaller margins accounting for delineation variation could be used. This could reduce radiotherapy related toxicity, such as skin effects and breast fibrosis, and compensate for the possibly larger volume delineated when using a hydrogel injection. Also, as shown in Fig. 1, some observers have smaller volume contoured compared to other. This would mean a lower volume treated using APBI and potentially an improvement of the treatment tolerance. Furthermore, by helping target definition in patients with low CVS, more patients may be eligible for more patient friendly APBI techniques as patients with a poorly defined cavity are generally excluded [15–17,39,40]. A gel with good MRI visibility could also be very useful in an era when new machines, including the MR-linac, are used for improved image guided radiotherapy (IGRT) [41].

An important caveat in breast radiotherapy target definition is the fact that the tumor bed needs treatment and does not necessarily match the lumpectomy cavity. The discussion about the volume to be treated lead the GEC-ESTRO to develop comprehensive contouring guidelines and recommends using the microscopic surgical margins in all directions to realize the expansion from seroma to clinical target volume (CTV). The hydrogel helps to better define the lumpectomy cavity, but still the contouring guidelines should be followed.

A limitation of the hydrogel intra-operative injection is that in 9 out of 21 cases the seroma as defined by the gel showed some leveling with fluid or dilution resulting in imprecise contours. Since the CT scan was performed on average 5.5 weeks after the surgery, we assume that post-operative healing, inflammation

and fluid production may have deteriorated the visibility of the gel. In such cases the observers have unanimously incorporated the diluted cavity into the target volume.

In our study patients with CVS scores below 3 had the most benefit from the hydrogel. To better select those patients who benefit the most from a hydrogel injection, a future direction would be to change the timing of the intervention to the moment of radiotherapy planning when the healing process is completed. This would also partly resolve some of the limitations caused by dilution of the gel as described above.

In conclusion, this study shows that the use of a radiopaque hydrogel during BCS enables breast surgeons to clearly demarcate the lumpectomy cavity, resulting in a high inter-observer agreement of radiotherapy target definition. This intervention is easy to perform and can easily blend into standard practice.

Conflict of interest

None.

Acknowledgements

The author wants to acknowledge the support of Peter van Gelder for proofreading the manuscript and Bas Schipaanboord for technical support analyzing the contours in MIM. The study was supported by a grant in kind from Augmenix Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2018.11.003>.

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