Acta Oncologica, 2009; 48: 487–494

informa
healthcare

REVIEW ARTICLE

Review of MammoSite brachytherapy: Advantages, disadvantages and clinical outcomes

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Abstract

Background. The MammoSite® radiotherapy system is an alternative treatment option for patients with early-stage breast cancer to overcome the longer schedules associated with external beam radiation therapy. The device is placed inside the breast surgical cavity and inflated with a combination of saline and radiographic contrast to completely fill the cavity. The treatment schedule for the MammoSite monotherapy is 34 Gy delivered in 10 fractions at 1.0 cm from the balloon surface with a minimum of 6 hours between fractions on the same day. *Material and methods***.** This review article presents the advantages, disadvantages, uncertainties and clinical outcomes associated with the MammoSite brachytherapy (MSB). *Results.* Potential advantages of MSB are: high localised dose with rapid falloff for normal tissue sparing, minimum delay between surgery and RT, catheter moves with breast, improved local control, no exposure to staff, likely side-effects reduction and potential cost/time saving (e.g. for country patients). The optimal cosmetic results depend on the balloon-to-skin distance. Good-to-excellent cosmetic results are achieved for patients with balloon-skin spacing of $\geq$7 mm. There have been very few published data regarding the long term tumour control and cosmesis associated with the MSB. The available data on the local control achieved with the MSB were comparable with other accelerated partial breast irradiation techniques. The contrast medium inside the balloon causes dose reduction at the prescription point. Current brachytherapy treatment planning systems (BTPS) do not take into account the increased photon attenuation due to high Z of contrast. Some BTPS predicted up to 10% higher dose near the balloon surface compared with Monte Carlo calculations using various contrast concentrations (5–25%). *Conclusion.* Initial clinical results have shown that the MammoSite device could be used as a sole radiation treatment for selected patients with early stage breast cancer providing good local control, minimal complication rate and excellent cosmesis.

Key Words: *Accelerated partial breast irradiation, brachytherapy, MammoSite*

Breast conserving therapy (BCT) has become an accepted alternative to mastectomy for treatment of patients with early stage breast cancer [1,2]. This technique has been reported to result in local control rates equivalent to that of mastectomy in patients with early stage breast cancer [3–5]. It consists of the removal of breast tumour surgically (lumpectomy) followed by 5–7 weeks of daily whole breast irradiation course [6,7]. During the standard radiotherapy procedure a total dose of 45–50 Gy is delivered to the entire breast [8,9]. However, the disadvantage of this approach is its prolonged time which may present obstacles for many patients, especially the elderly and those who live far away from the radiotherapy facility [10].

To tackle this problem, accelerated partial breast irradiation (APBI) has been introduced as an alternative treatment method for patients with early stage breast cancer. One form of APBI uses interstitial brachytherapy (IB) implant technique [1,9,11–13]. With this technique, it became possible to give a large dose per fraction to a limited portion of breast tissue adjacent to the lumpectomy cavity in a shorter treatment time. However, IB is not trivial to deliver and is only provided by a limited number of cancer centres [14–16]. Moreover, the treatment planning

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(Received 14 March 2008; accepted 8 October 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802537916

with this technique is time-consuming and requires experienced staff [17].

In response, a new approach to breast brachytherapy has been developed in recent years [18]. This novel technique uses the MammoSite® brachytherapy (MSB) system (Cytyc, Marlborough, MA) as a sole radiation treatment for patients with early stage breast cancer following lumpectomy. It can also be used as a boost in conjunction with external beam radiotherapy (EBRT). It consists of a small balloon connected to an inflation channel and a catheter for the passage of a high dose rate brachytherapy source (Ir-192) shown in Figure 1. The device is placed in the lumpectomy cavity during or following breast surgery [18]. The MammoSite balloon is inflated with the sterile saline containing a small amount of radiographic contrast to a size that both completely fills the cavity and ensures conformance of the tissue to the balloon [19,20]. Computed Tomography (CT) scan is obtained to assess balloon conformance to the lumpectomy cavity and to determine the distance from the surface of the balloon to the skin, the symmetry, diameter of the inflated balloon, the planning target volume and the dose distribution [18]. The treatment with the MammoSite device is generally 34 Gy delivered in 10 fractions (3.4 Gy /fraction twice daily) at 1.0 cm from the balloon surface with a minimum of 6 hours between fractions on the same day [18,21]. There are recommendations regarding the patient selection for the MammoSite treatment. Generally, it is used for treatment of patients diagnosed with ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC) and a primary tumour of size $\leq$3 cm.

The MammoSite brachytherapy device has been commercially available since 2002. The first published study on the applicator use has demonstrated that both device insertion and performance are simple and efficient [18]. Also, the treatment planning time may be decreased to 25 minutes [22]. Other advantages of the MSB technique have included better dose homogeneity, sparing of normal tissues, less radiation exposure to the staff and potential reduction in acute and late side effects. In the past 5 years a few studies investigated various aspects of the MammoSite technique, including the volume of breast tissue treated compared to IB and EBRT techniques. Others have described the dose perturbation caused by the radiographic contrast in the balloon. Recently, clinical results have appeared reporting on the cosmetic outcomes and tumour control for patients treated with the MammoSite as a sole radiation method. This review article summarizes the advantages, disadvantages, uncertainties and clinical outcomes associated with the MSB radiation system.

Figure 1. The MammoSite ® Radiation Therapy System, courtesy of Cytyc Corporation and affiliates.

Dosimetry of MammoSite

Limited publications have evaluated the dosimetry achieved with the MSB [17,18,23–25]. Edmundson et al. [18] reported the first study on the MSB dose distribution. Eight patients were treated and a CT scan of each patient was used to determine the treatment parameters, namely the balloon radius, balloon symmetry, the planning target volume (PTV) and the distance from the balloon surface to the skin. The MammoSite dosimetric data was analysed and compared to a similar group of patients treated with IB at the same institution. The mean PTV of the MammoSite patients was 112.1 cm^3 compared with 98.3 cm^3 for IB patients. The MSB provided better PTV coverage compared to that achieved with IB. The D_{90}, the minimum dose to 90% of the PTV, was calculated for both techniques. The mean values were 90.0% and 69.8% of the total dose for the MammoSite and the IB methods respectively. The MSB resulted in significant improvement in dose distribution. However, the MammoSite device with the balloon radius larger than 3.0 cm was found to result in longer treatment times and to give rise to higher doses to the normal structures, such as the heart and the lungs. As a result, a cavity with volume of 50 cm^3 represents an upper limit on the size of the cavity that can be treated with the MammoSite balloon [18].

Dickler et al. [23] presented results on the volume of breast tissue treated with the MammoSite applicator. The study included 21 patients with early stage breast cancer. The volume of the treated breast tissue was constructed on the basis of scans of the lumpectomy cavity of each patient both with and without the inflated balloon. It was found that the volume of breast tissue treated by the MammoSite device was equal to the volume encompassed by a margin of 1.6 cm around the empty lumpectomy cavity. This is comparable with IB which treats a 1–2 cm of tissue margin around the lumpectomy cavity.

Major et al. [17] reported a dosimetric comparison between treatment plans of IB and MSB patients. The comparison included 17 and 24 patients treated with IB and MSB respectively. The average volume and dose parameters for IB and MSB techniques are listed in Table I. The plans for all patients were based on CT images, and the dose distributions were evaluated using dose volume histograms (DVHs). The average volume of PTV was considerably higher for MSB than IB patients at 109.6 cm^3 and 63.4 cm^3, respectively. The small volume of the PTV for IB patients is due to the safety margin of 1.0 cm used around the lumpectomy cavity. The volume of the PTV receiving twice the prescribed dose ($V_{200\%}$) was less for the MSB patients. The dose distribution was much more conformal in the MSB than IB. However, the definitions of the PTV were different in the IB and MSB groups. In IB an individual margin can be used in different directions, while in MSB a uniform margin of 1.0 cm from the balloon surface is used. The doses to the heart were not significantly different between the two groups. But the maximum point dose to the lung was higher in MSB plans compared to IB plans. Overall the MSB has produced acceptable dosimetry, but longer follow-up time was recommended to evaluate its clinical efficacy.

Weed et al. [24] reported the first single-institutional dosimetric comparison of patients treated with three APBI techniques: IB, MSB and 3D Conformal Radiation Therapy (3D-CRT). DVHs were used to evaluate the dose coverage of the PTV and the doses to normal structures including the ipsilateral breast, ipsilateral lung, and heart. A summary of patient dose and volume information for all three techniques is presented in Table II. Coverage of the PTV varied according to the technique used and the margin drawn around the lumpectomy cavity. The 3D-CRT offered the best PTV coverage. The average PTV volume for the 3D-CRT patients was twice larger than the average PTV for the MSB patients and slightly larger than the average PTV for the IB patients. The percentage of the PTV receiving 100% of the prescribed dose was 58% in the IB method compared with 76% and 94% with the MSB and 3D-CRT techniques respectively. The percentage of the PTV receiving 90% of the prescribed dose was 68%, 91% and 100% for the IB, the MSB and 3D-CRT techniques respectively.

Table I. Average volume and dose parameters for IB and MSB patients [17].

Variables	MSB	IB
V_{PTV} (cc)	109.6	63.4
V_{90} (%)	96	92
V_{100} (%)	88	87
V_{150} (%)	27	55
V_{200} (%)	3	32
D_{90} (%)	99	94
D_{min} (%)	67	58
D_{lung} $(\%)_{max}$	66	55
D_{heart} $(\%)_{max}$	27	29

Table II. Patient characteristics including total dose, volume of lumpectomy cavity, volume of ipsilateral breast, volume of ipsilateral lung and heart volume [24].

Variables	IB	MSB	3D-CRT
Number of patients	10	10	10
Total dose (cGy)	3200	3400	3850
Average lumpectomy cavity (cc)	38	53	24
Range (cc)	5-101	37-70	8-44
Average PTV volume (cc)	192	107	237
Range (cc)	97-357	83-125	104-380
PTV expansion (cm)	1.5	1	1 + CTV (1.5)
Average breast volume (cc)	1920	1628	1568
Range (cc)	1059-2654	1147-2729	633-2569
Average lung volume (cc)	1116	1404	1355
Average heart volume (cc)	563	568	584

Both brachytherapy techniques delivered significantly less dose to the normal breast tissue as compared with the 3D-CRT [24]. For example, the percentage volume of the ipsilateral breast receiving 100% of the prescribed dose was 5%, 10% and 24% for the MSB, IB and 3D-CRT patients, respectively. However, both brachytherapy methods treated higher portion of the breast volume above 115% of the prescribed dose compared with the 3D-CRT. For instance, the MSB and IB treated 4% and 5% of the breast volume to 115% of the prescribed dose, respectively while 0% of the breast volume received 115% of the prescribed dose with the 3D-CRT. All three techniques resulted in small dose to normal structures. The average volume of the ipsilateral lung receiving 10% and 20% of the prescribed dose was 9% and 5% for 3D-CRT compared with 3% and 0% for IB and 4% and 0% for the MSB patients. The average volume of the heart receiving 10% of the prescribed dose was 1% for each of the three techniques.

The above study concluded that the MammoSite device consistently provided better dose coverage of the PTV as compared to IB. But the 3D-CRT offered better coverage of the PTV in comparison to either of the brachytherapy techniques. However,

this resulted in a higher dose to the normal breast tissues and lung. As a result, the optimal partial breast irradiation technique is a clinical decision. The shortcoming of the study is that it does not compare dosimetry in identical patient data sets. The patients representing the three different treatment groups were different which can make the dosimetric comparison less straightforward.

Khan et al. [25] presented dosimetric comparison of three different methods of APBI: The MSB, 3D-CRT and Intensity Modulated Radiation Therapy (IMRT). It consisted of 15 patients who underwent BCT. With the use of CT images, plans were developed for each patient using each of the three techniques. A summary of the dosimetric results for the various techniques is summarized in Table III. The volume of the PTV was smaller in MSB plans than in 3D-CRT and IMRT plans. This is attributed to the 2.5 cm margin which was used around the lumpectomy cavity to generate the PTV for both 3D-CRT and IMRT methods. All three groups had low volume of the lung receiving 30% of the prescribed dose, but the IMRT patients had the lowest value. An interesting result from the study is that the MSB technique resulted in significantly higher dose to the heart (V_5) as compared to both 3D-CRT and IMRT method for the ten patients with left-sided tumours. This is because, as opposed to MSB treatment planning, the heart is contoured as an organ at risk in both 3D-CRT and IMRT plans and the dose delivered can thus be constrained and optimized. Both 3D-CRT and IMRT methods have the advantage of not requiring a placement of foreign object inside the patient. However, the difficulty of identifying the cavity in certain patients, respiratory motion and patient setup may be of concern when using 3D-CRT and IMRT techniques. On the other hand, these issues are not significant with the use of the MSB. It was concluded that the choice of optimal PBI method is complex and requires both the doctor's decision and suitable patient selection.

Table III. Dosimetric comparison of 3 different APBI techniques [25].

Variables	MSB	3DCRT	IMRT
PTV volume (cc)	94.3	184.3	184.3
V_{110} (%)	84.2	0.99	0.8
V_{100} (%)	94.9	92.3	93.7
V_{95} (%)	97.9	99.9	99.9
V_{90} (%)	99.3	99.9	100.0
Ipsilateral breast V_{50} (%)	29.2	55.8	46.2
Ipsilateral lung V_{30} (%)	5.4	6.7	1.9
Heart V_5 (%)	11.6	4.1	1.2

Balloon contrast concentration

Once in place, the MammoSite device is inflated to a size that fills the surgical cavity using saline and an amount of radiographic contrast. CT scans are then obtained and the treatment plan is developed. Current available BTPS (e.g Plato, Nucletron) perform dosimetry calculations according to the recommendations of the AAPM TG-43 protocol [26]. This protocol assumes that the high dose rate brachytherapy source is located in water medium. Since the contrast medium contains elements with high atomic number (iodine, $Z = 53$), the balloon is no longer tissue or water equivalent. Thus, the BTPS do not accurately predict the dose at the balloon surface. Several studies have used Monte Carlo (MC) simulations to determine the dose reduction factor corresponding to a range of contrast concentrations [19,20,27–29]. In Table IV, a summary of the dose reduction factors at 1 cm from the balloon surface for balloon radii of 2 & 3 cm and several contrast concentrations determined in different studies is presented.

Mitra et al. [27] performed measurements of the dose perturbations resulting from the use of various contrast concentrations (5–25%). The BTPS predicted about 9% higher dose near the balloon surface compared with measured values. This was attributed to the lack of inhomogeneity corrections in the BTPS. Ye et al. [28] performed MC calculations and found that a 25% contrast concentrations inside the balloon resulted in up to 5% dose reduction at the surface of the balloon. Other investigators reported that, with a 4% contrast concentration, the BTPS overestimated the dose at the balloon surface by about 10% as compared with MC calculations [29]. These studies have demonstrated that the dose rate reduction depends on the concentration of contrast material. It has been suggested that limiting the contrast concentration to 10% would ensure less than 3% reduction in the prescription dose, regardless of the balloon size [19].

Table IV. Dose perturbation factors using MC calculations at 1 cm from the balloon surface for various balloon radii and contrast concentration percentages [19,20].

Contrast concentration(%)	Dose reduction factor Balloon radius (cm)	
	2	3
0	1	1
5	0.992-0.995	0.986-0.989
10	0.984-0.990	0.971-0.982
25	0.960-0.978	0.943-0.959
50	0.954	0.925
75	0.937	0.898
100	0.919	0.875

MammoSite and cosmetic outcomes

The two most important factors for achieving treatment effectiveness and optimal cosmetic results are balloon cavity conformance and skin-to-balloon surface distance. The former is essential in order to achieve good dose homogeneity within the PTV. The latter is for restraining the maximum skin dose. A minimum distance between the balloon and the skin of 5 mm was chosen to keep the skin dose less than 150% of the prescribed dose [18,30]. However, recent publications recommend a balloon-to-skin distance larger than 7 mm to achieve excellent cosmetic results [31,32]. The clinical results of recent publications using the MSB as sole radiation treatment following lumpectomy are summarized in Table V. For example, Dragun et al. [32] reported excellent cosmetic results in 68.9%, good in 21.1%, fair in 8.9% and poor in 1.1% of 100 patients treated with the MammoSite device at a median follow-up of 2 years. No breast tumour recurrence was reported. Overall, the excellent cosmetic results were associated with a balloon-to-skin distance larger than 7 mm.

Jeruss et al. [42] reported clinical results of 169 patients who had breast cancer treatment with the MammoSite balloon device. The follow-up data was available for 158 patients. The average length of the follow-up was more than seven months. Patients with the balloon-to-skin distance $\geq$7 mm had the best cosmetic results and less skin damage. These findings were confirmed using data on 43 patients who had a follow-up period of at least one year. No patient in the study has experienced a recurrence of the disease.

Long term follow-up data

There have been very few published data regarding the long term tumour control and cosmesis associated with the MSB. Chao et al. [44] presented the results of eighty patients treated with the MammoSite applicator. Up to 88.2% of patients were found to have good/excellent cosmetic results at 3-year follow-up. Ipsilateral breast-tumour recurrence occurred in two patients (2.5%) Both recurrences occurred within 12 months after completion of the MammoSite treatment. The 3-year disease-free survival rate for all patients was 95.8%. At 24 months follow-up, an increased balloon-to-skin spacing $\geq$7 mm was associated with high occurrence of good-excellent cosmetic results, highlighting the importance of the distance from the balloon surface to skin to avoid excessive dose to the skin. The 3-year follow-up results demonstrated that the MammoSite treatment outcomes were similar to those observed with IB at the same follow-up length.

Chen et al. [45] reported 7.1% of treatment failures among 70 patients treated with the MammoSite technique at a median follow-up time of 26.1 months. The tumour recurrence for one case was directly adjacent to surgical bed and three cases were at more than 2 cm away from the original surgical bed. Benitez et al. [46] presented the results of 5.5-year follow-up of 36 patients treated with the MSB. The cosmetic outcomes were good /excellent in 83.3% of the followed patients. There were no local recurrences at either the tumour bed or elsewhere in the breast for all 36 patients. The study concluded that the 5-year local recurrence using the MammoSite balloon in carefully selected patients was comparable to the 5-year data achieved with IB and EBRT.

The available 3-5 year results can serve as an indicator of the adequacy of the MammoSite treatment method in terms of tumour control in comparison with other APBI techniques. However, further data is still needed to document its long term efficacy.

Table V. Clinical results of cosmetic outcomes and tumour recurrence using the MSB.

Author	# of patients	Average follow-up (months)	Good/ excellent cosmetic results (%)	Skin distance (mm)	Skin dose/ fraction (cGy)	Tumour recurrence (%)
Dragun et al. [32]	100	24	21-69	7-8		0
Keisch et al. [33]	43	21	88	>7		0
Keisch et al. [34]	43	29	84	>7		0
Shah et al. [36]	28	19	93	≥ 5		0
Dickler et al. [37]	30	13	93	7-15	354-422	0
DiFronz et al. [38]	40	13	97	>7		0
Harperet al. [39]	30	7	20-73	4-14	130-558	0
Vicin et al. [40]	248	12	92	≥ 7		0.1
Benitez et al. [41]	100	9.5	98	7-13		2
Jeruss et al. [42]	158	12	88	>7		0
Sadeghi et al. [43]	67	13	96	7-15	56-488	0

MammoSite treatment complications

Limited information is available in the literature regarding the toxicities associated with the MSB. Richards et al. [35] reported the acute toxicities of 27 patients treated with the MammoSite device as the sole method of radiotherapy. The median follow-up was 11 months. No acute toxicities were reported during the 5 days of treatment however 25% of the patients developed bright erythema and patchy moist desquamation, 7% developed confluent moist desquamation within the first 4 weeks but healed by week 12 and 16% of the treated patients developed infections. Harper et al. [39] assessed the acute complications of 37 patients on the day of the treatment completion and four weeks after the course of the treatment. As many as 93.3% of the patients were happy with the MammoSite therapy however 5.4% (2 patients) experienced Grade 2 toxicity, 2.7% (1 patient) experienced Grade 3 toxicity, 16.2% (6 patients) developed wound infections and 32.4% (12 patients) developed seromas. Sadeghi et al. [43] examined the dose delivered to the skin and the surrounding tissues in 67 patients treated with the MSB. Fifty six percent of the patients experienced no skin reaction at a median follow-up of 13 months, 35% developed erythema but it disappeared over several weeks, 4 (6%) patients had dry desquamation and 2 (3%) patients experienced moist desquamation, and received skin dose greater than 4.10 Gy per fraction. Agawal et al. [47] assessed acute toxicities in 100 patients treated with the MSB. Persistent seroma was observed in 26% of the patients with a follow-up of 6 months. The study concluded that the development of seroma may be attributed to the delivery of high radiation doses to the surgical cavity margin. Evans et al. [48] reported the risk of development of seroma in 38 patients. Persistent seroma was seen in 68.4% of the patients with a follow-up of more than 6 months. Of the patients with persistent seroma, 46% experienced some pain in the breast during the follow-up period. However, only 19.2% of those patients had these symptoms persisted at their last follow-up (median of 15.8 months) examination. Overall, the results of the studies of the acute complications associated with the MammoSite method are encouraging but these observations need to be validated with more published clinical data.

Conclusions

Previous investigators have demonstrated that the MammoSite device insertion into the patient and treatment execution is easy and efficient. In the studies reported, coverage of the PTV varied according to the radiation technique used and the definition of adequate coverage used. However, in general the MSB device produced better coverage of the PTV compared to IB implants. The coverage of the PTV was better with 3D-CRT, resulting however in a higher dose to normal breast tissue than the MammoSite brachytherapy technique.

For imaging purposes, the MammoSite balloon is filled with saline and radiographic contrast. The amount of radiographic contrast varies from one study to another for several reasons including oncologist preference and institutional protocol. The presence of the contrast medium inside the balloon can cause reduction in the dose at the prescription point depending on its concentration. The BTPS currently in clinical use do not take into account the attenuation of the photons caused by the contrast medium. Some BTPS predicted up to 10% higher dose near the balloon surface compared with MC calculations for contrast concentrations between 5–25%. As a result the amount of contrast medium used inside the balloon should be minimized to avoid a potentially significant reduction in the delivered dose.

It appears that two factors may limit the use of the MSB device. The conformance of the balloon to the cavity is essential to assure appropriate dosimetry. Additionally, the distance between the balloon and the skin appears to be the most important factor for achieving optimal cosmetic results. Cosmetic results were good-to-excellent in most patients with balloon-skin spacing of $\geq$7 mm.

The endpoint of the MammoSite treatment technique as with any other radiotherapy modality is to achieve high tumour control probability and minimal normal tissue complications. Existing clinical findings have demonstrated highly acceptable outcomes with the MSB applicator regarding tumour control, acute complications and cosmetic results. The data coming from the published clinical trials with an average follow-up of 16 months have neither reported tumour recurrence nor normal tissue complications among the treated patients. This indicates that smaller PTV coverage in MSB does not represent a significant reduction in the treatment outcomes while offering better patient comfort (shorter treatment time) and cosmesis. The currently available long term data on the MSB tumour control were comparable with other APBI techniques. In conclusion, the MammoSite is a suitable technique for APBI. It offers good outcomes and shorter treatment schedules.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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