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REVIEW

Photodynamic therapy of the intact breast

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Summary As breast cancer is diagnosed in over a million patients a year it is a significant oncological issue. Treatment paradigms have shifted to emphasize breast preservation protocols. However, due to a lack of equipment and facilities this option is only rarely offered to poverty stricken patients and those in the developing world. Photodynamic therapy may play a role in allowing for greater breast conservation based in part on the emerging success of partial breast radiation. This paper will review the rationale behind and technical aspects for intact breast photodynamic therapy.

Contents

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Introduction

With over one million patients diagnosed with breast cancer each year, the scope of this medical problem cannot be under-estimated [1]. Until prevention is successful and implemented worldwide, therapeutic intervention is the strategic mainstay. Additionally, since this anatomical region has unique psychological and physiological attributes in society and to individuals, breast conservation and preservation has become a fundamental component of therapy.

Importantly, patients in many areas of the world, particularly those in poverty do not often have access to facilities that allow for breast preservation therapy [2,3].

To that end, photodynamic therapy (PDT) may play an important part of breast preservation strategies. PDT has an impressive record of tumor elimination with functional preservation [4]. PDT also has been successful as a cost effective modality [5]. Of particular relevance is that PDT can be brought on line in developing regions of the world in which state of the art equipment may be lacking, thus bringing function sparing interventions to an audience who might never have been offered this option [6]. Further, PDT has achieved an impressive record in the control of recurrent breast cancer that has failed conventional therapy [7,8]. Perhaps, then PDT should play a role in breast preservation.

This paper will review the rational and potential benefits of PDT as a part of primary breast cancer therapy. Suggested intervention strategies will be outlined.

Current strategies to breast conservation

To understand the potential roles for PDT in breast conservation therapy, it is worthy to review the components and trends in the standard interventions used worldwide. These include surgical and radiotherapy aspects for the breast and regional nodes as well as indications for systemic therapy. All might be effected by the use and timing of PDT.

Surgery

Nowhere else has the Halstedian model of malignancy been more entrenched than in breast cancer [9,10]. Classically it was heresy to consider anything less than radical mastectomy as a curative or even palliative intervention. Despite the fact this Halstedian concept of orderly spread of disease seems at odds with the clinical reality of these tumors, relatively rapidly after its introduction, the Halstead radical mastectomy became the gold standard of treatment. Conceptually, the surgeon would excise the primary tumor and the tissue it could grow into as well as the next echelon of spread, the lymphatics. A successful radical mastectomy would remove the entire breast and associated chest wall musculature and all nodes in the axilla (levels I, II, and III). For a time even more extensive surgery including excision of the internal mammary, infraclavicular and supraclavicular nodes was popular. Unfortunately, even if local control was achieved, many patients with extensive primary tumors failed distantly and succumbed to disease. Further, the morbidity associated with this surgery was severe. Notably, lymphedema usually resulted in the loss of most arm mobility on the operated upon side. Fortunately for patients, modified versions of this surgery eventually become the standard of care [11]. These operations were less extensive, leaving chest wall musculature and lymphatic pathways, so functional morbidity was dramatically reduced without survival compromise. With the realization that less can sometimes be more, randomized trials comparing quadrantectomy and lumpectomy to mastectomy followed, again, showing no survival compromise with significantly less functional morbidity [12,13]. Clearly, a trend to as minimally invasive removal of a breast tumor with retention of as much breast tissue as possible has now appeared to become the surgical standard.

Radiation therapy

Radiation therapy for breast cancer has also evolved. Initially, radiation portals followed the

Halstedian rules. The entire breast or chest wall, axilla, supraclavicular and internal mammary chains were irradiated. Long-term follow up revealed that when these fields were added postoperatively, improved local control was seen as was additional morbidity [14]. With the early technology available acute morbidity to the skin was significant and often painful. Chronic morbidity including worsening of lymphedema, fibrosis of the skin, rib fractures, pulmonary damage and cardiac disease induction were significant and all too common. As surgery moved to less invasive procedures so did radiation. By the 1980s, internal mammary fields, often the cause of most cardiac morbidity were rarely used. Further, dissected axillary regions were not routinely radiated so lymphedema was much milder. As morbidity declined, this allowed radiation therapy to be employed routinely in breast cancer.

Perhaps the landmark change occurred with the National Surgical Adjuvant Breast and Bowel Project (NSABP) confirmation of European trends [12,13]. Radiation to the breast following lumpectomy offered similar local control and survival when compared to mastectomy. Further, radiation therapy and lumpectomy allowed retention of a cosmetically acceptable intact breast, something that should never be under-estimated both physiologically and psychologically. Thus, based on well designed, large randomized clinical trials the concept of breast preservation as the standard treatment for most breast cancers was born. With improved technology, particularly conformal radiation and intensity modulated radiation therapy, where radiation dose to normal tissue are severely restricted outstanding clinical and cosmetic results can be obtained with very few patients experiencing chronic treatment related morbidity [15]. Again the trend with radiation therapy is for as cosmetically pleasing treatment as possible to allow retention of an intact breast.

Axilla and lymphatics

The axilla is critically important to both diagnostic and prognostic aspects of breast cancer treatment [16]. Axillary metastases classically bode for systemic interventions. Thus, it is critical to current therapeutic evaluation to understand the status of axillary nodes. Further, axillary dissection can be therapeutic and prevent local progression and failure in this anatomy. However, axillary exploration can be highly morbid. Recently with the development and refinement of sentinel node biopsy, a new age in breast treatment has arisen [17]. No longer does every patient undergo axillary dissection with its risk of morbidity. Rather a sentinel node procedure is extremely well tolerated and generally results in no functional loss. The vast majority of patients diagnosed today in the industrialized world will have a negative sentinel node and be spared axillary dissection. Those with a positive finding (about 15% of all patients) will have a level I/II dissection which has a 5% or less chance of clinically significant morbidity. The internal mammary and infraclavicular nodes are now rarely dissected; however, with improved surgical techniques they too can be evaluated without the classical high morbidity seen a century ago. Again, the trend is to a less invasive and less morbid intervention in the nodal basins.

Systemic therapy

Appropriate systemic therapy is a key ingredient to maximizing survival [18]. Currently, systemic therapy consists of a cocktail of chemotherapeutic agents, hormonal therapy and biological agents. Optimizing these choices for an individual patient continues to evolve. The treatment paradigm employs the age of the patient, size of primary tumor, histological characteristics, margins of resection, axillary status, and patient preference among other parameters. It appears that currently, the Estrogen/Progesterone receptor status and HER-2 neu plays a most critical role in defining the type of adjuvant therapy indicated. Likely the near future will show micro-array technology as a means to enhance accuracy of adjuvant therapy. However, as long as the histological and biological aspects of the tumor are required for systemic therapy evaluation and as long as the status of resection margins are important considerations, local interventions must respect and not interfere with retrieval of these data.

Emerging trends for breast conservation

One startling aspect of breast cancer is that local control of tumor may have limited impact on survival. When followed to 20 years, patients undergoing mastectomy or lumpectomy or lumpectomy and radiation therapy have identical survival curves, though lumpectomy patients alone experience a 25% local failure rate in the breast. In contrast with longer follow up to 30 years the addition of radiation therapy to mastectomy did offer improved survival of perhaps 5% [14]. However, recent meta analysis does confirm improved survival with the addition of radiation. It is potentially important to note that this is with whole breast or chest wall radiation [19]. Given the huge number of patients so diagnosed this should be relevant. Significantly, as patients are now diagnosed earlier and younger via screening programs and are more commonly expected to attain old age, maximizing local control is a relevant strategy to improve survival. Maximizing local control is also highly relevant as patients do not appreciate a cancer returning in a treated region.

Using the NSABP data as a model, lumpectomy even with clear resection margins as was required by this trial, has a continuous risk of local failure of about 1—2% per year [13]. The addition of whole breast radiation therapy, even months after surgery, cuts this risk dramatically. This has been the basis for whole breast radiotherapy following lumpectomy as the standard of care for the last two decades. A closer examination revealed that for most patients who fail lumpectomy alone do so at or adjacent to the original surgical site [20]. Based on this, a paradigm shift has occurred in breast radiotherapy. Essentially, radiation therapy is now delivered to the resection bed with margin without any attempt at coverage of the remaining mammary tissue. Several techniques are available with the most popular being direct implant to the lumpectomy bed generally using after loading radioactive sources via a breast brachytherapy balloon catheter. In select centers an intra-operative dose of radiation directly to the lumpectomy site is offered.

All these techniques can be used as a boost to whole breast external beam radiation, but in reality the current trend is for patients to have this as a stand alone treatment. The rationale behind this local treatment is based on a number of arguments [20]. As mentioned, since most failure is local perhaps all that is needed is local treatment. As external beam radiation therapy has morbidity to skin, lung, and heart, more localized treatment may be beneficial. Further, whole breast radiation therapy is time consuming and may require 6 weeks of daily visits which may not be possible for all patients.

Currently available partial breast adjuvant interventions

Despite no randomized data, partial breast irradiation has grown in popularity generally for the above-mentioned reasons. With follow up measured in months, early reports have yielded high local control rates [21,22]. Further, reported morbidity may be minimal with cosmetically acceptable outcomes noted [21,22]. By examining the emerging partial breast techniques we can explore an optimal photodynamic therapy intervention.

Partial breast external beam therapy

A localized external beam field to the lumpectomy bed with margin rather than whole breast radiotherapy is employed [23]. The advantage is that external beam is accomplished post surgery so margin status and histology are defined. As a smaller volume is treated fewer visits are required. A limited amount of breast tissue is irradiated so morbidity should be less. Disadvantages include breast motion from breathing which will make targeting hard and geographic miss possible. Multiple treatment visits are required and significant volumes of normal tissue are radiated. The high dose per fraction increases the risk of fibrosis making long-term cosmesis a concern.

Permanent implant breast brachytherapy

A permanent radioactive set of sources are placed in the breast lumpectomy site [24]. The advantage is this procedure is done post lumpectomy so margin status is available. This is a rapid approach as the procedure requires one visit for planning and one for seed insertion. The seeds are placed into the surgery site so targeting is accurate. Disadvantages include providing radiation protection particularly for family members, small children and visitors. Travel restrictions are required. The potential for seed motion from healing and swelling will alter dosimetry. Cosmesis may be a concern as high doses to small volumes can lead to fibrosis, even years post implant. Potential dose to thyroid, heart, lung and other organs may be significant. Interference from seeds for mammogram and other diagnostic studies may make for difficult follow up.

Intra-operative external beam radiation therapy

At the time of lumpectomy an intra-operative linear accelerators delivers radiation therapy to the resection bed [21,25]. The advantage is that a single fraction treatment is accomplished at the same sitting as lumpectomy. Disadvantages include the lack of final histology and evaluation of margins. A limited volume receiving the prescribed radiation dose meaning overdosage or underdosage to critical regions is possible. Also, these are very expensive machines and are of limited availability. Intra-operative treatment can also be used in conjunction with external beam therapy. The initial intra-operative fraction replaces the boost from electron beam [25].

Balloon after loading high dose rate brachytherapy

A progressively more popular form of partial breast radiation is by remote after loading HDR [26,27]. A commercially available balloon, the Mammosite, is temporarily implanted into the lumpectomy cavity. Following dosimetric calculation, radiation is delivered to the lumpectomy cavity with margin. The advantage of this technique is that since the balloon is in the lumpectomy cavity, geographic miss of radiation is unlikely. Further, as the balloon is inflated for a custom fit it should end up being centered in the surgical bed for a homogenous dose of radiation. Disadvantages include multiple treatment visits, balloon failure, and morbidity to the skin from high radiation dose. The extreme cost of the HDR brachytherapy unit is a significant disadvantage as well.

Multicatheter after loading partial breast irradiation

In this technique a template is used to insert several catheters around the lumpectomy site [28]. Then, after appropriate dosimetric calculation radiation sources are placed into the catheters. Generally multiple visits over a 1-week period allows for radiation delivery. The catheter stay in place until radiation is complete. The advantages and disadvantages of this technique are similar to balloon type brachytherapy. However, the multiple catheters that are placed through the skin likely diminish cosmetic outcome.

Technical considerations

It is worthy to review the technical aspects of partial breast brachytherapy as the lessons learned here would likely translate into PDT for this indication. For example, originally balloon type partial breast radiation therapy had the apparatus placed during the lumpectomy surgery [29]. While technically feasible and with the benefit of a single procedure severe shortcomings exist with this approach. Most importantly, clear resection margins are an important prognostic factor in local control. As many as 25% of patients undergoing lumpectomy need re-excision due to close or involved margins. Having a balloon or other apparatus in the surgical bed that has delivered treatment and perhaps altered anatomy makes re-excision difficult if not impossible. Further, with post operative swelling or hematoma formation, optimal dosimetry is difficult in some patients. In addition, it became readily apparent that should the radioactive sources be too close to the skin, breakdown and fibrosis of the skin is possible. Therefore, some patients could not undergo treatment even though the device was placed [30].

For those reasons, most brachytherapy procedures now take place at a second sitting after lumpectomy. Prior to brachytherapy, the final pathology is evaluated as is the actual location of the lumpectomy bed relative to the skin. For patients still a candidate for this procedure, an ultrasound guided technique is used in the balloon type procedure. After local anesthesia to the surgical bed and skin, a metal trochar is inserted into the lumpectomy site under ultrasound guidance. Usually this trochar incision is made lateral to the lumpectomy site and the trochar is brought into the tumor bed. The balloon catheter is then inserted through the trochar track and the balloon inflated. Upon confirmation by CT scan of placement and volume, dosimetric calculations are undertaken and radiation therapy delivered. It should be noted in a series of 1400 patients undergoing the procedure, 9% were unable to undergo radiation therapy due to technical difficulties [29,30]. Other series report similar number of patients cannot complete this therapy [31,32]. Interestingly, in an analysis of 1419 patients undergoing balloon brachytherapy the quality of cosmesis continues to decline with longer follow up [29,30].

Morbidity of interstitial type of radiation delivery

Leaving indwelling catheters or the Mammosite apparatus in place for 1—2 weeks required to complete radiation therapy is associated with infection which ranges from 5 to 30% depending on the study and techniques [29—32]. Seromas and hematomas are also possible. The actual radiation results in erythema of various degrees of intensity as well as the potential for fibrosis. A key risk factor is the distance of the radiation dose to the skin itself. Actual placement of the needles or balloon is also associated with pain unless the patient is under general anesthesia. Pain is also reported for a long as the apparatus are in place.

Photodynamic therapy—proof of principle

As partial breast radiation has emerged as a treatment option and as other means of local treatment such as radio frequency ablation, focused ultrasound and laser based ablation have been attempted to intact primary breast tumors, it would seem then that partial breast photodynamic therapy might become a treatment option as well. PDT has a long history of successful treatment of cutaneous lesions [7]. Of particular note is the ability of PDT to treat breast cancer recurrences that manifest on the chest wall. All breast PDT series that follow required histological confirmation for these lesions. It appears then that the treated lesions retained histopathological features consistent with the breast primary. Therefore, PDT to the primary tumor might be successful. Several series employing Photofrin® at widely disparate drug doses and light doses show excellent local response rates [33—36]. By employing relatively low doses of drug more selectivity between tumor and normal tissue reactions was possible which could have significant ramifications in intact breast treatment. Other photosensitizers have also shown response, though in smaller series. Foscan® PDT had high response rates but also high normal tissue morbidity in a trial employing relatively high drug and light doses [37]. Purlytin® also showed potential excellent control for these lesions with good normal tissue recovery [38].

In addition, a limited literature exists in which primary mammary lesions such as Paget's disease will fluoresce following photosensitizer infusion. This again shows the potential for these lesions to concentrate drug for primary treatment [39].

PDT for intact breast cancer treatment

The rationale for PDT as a means to increase local control post lumpectomy is no different than for radiation. Theoretically, local failure is due to residual tumor cell growth following excision or perhaps stem tumor cells that are activated post surgical excision. By delivering PDT to the tumor bed with 1—2 cm margin (the volume generally dosed with radiation therapy) local control may be increased. By using non ionizing therapy the long-term complications and risks of second malignancy induction is eliminated. As currently practiced partial breast radiation therapy usually requires expensive after loading high dose rate units or intra op units. These are fiscally difficult expenditures particularly in the developing world. PDT using laser or light emitting diode sources could be more cost effective. Balloon based brachytherapy usually also requires 10 visits so is relatively time consuming as compared to a single PDT visit.

Theoretically, PDT could be offered in a single visit. Delivering PDT at the time of the lumpectomy does indeed minimize treatment time. However, this suffers from the potential drawbacks of not having defined or clear resection margins. If PDT was successful in eliminating residual gross or microscopic tumor then perhaps clear resection margins would not be as important as it appears to be with the use of external beam radiation.

More likely intact breast PDT should follow the emerging trends from Mammosite brachytherapy. Currently, most patients come back for a second visit in which adjuvant treatment is delivered. This is due mainly to ensure negative margins of resection and confirmation of histological characteristics and importantly anatomical consideration to see if the lumpectomy site is amicable to local treatment.

Under local anesthesia, in the office, the balloon catheter is placed via ultrasound. If instead of radiation, illumination were to occur, successful PDT could be accomplished. In contrast to the 10 visits for radiation therapy, one simple PDT treatment could ensue. As the catheter is in place under image guidance, risk for geographic miss should be minimal.

The optimal drug and its dosimetry are not yet defined. Currently available photosensitizes have shown significant response for recurrent disease but not as primary therapy. Drug dose, light dose and drug to illumination interval based on published data could serve as a guideline for clinical trials.

PDT treatment paradigms for breast conservation

PDT could fit into several treatment paradigms. The relative merits and drawbacks are outlined.

PDT as a boost to whole breast radiotherapy

No randomized trials have been published showing that whole breast radiotherapy should be abandoned or even eliminated for any patient undergoing breast conservation therapy. Quite often whole breast radiation therapy is delayed a month post lumpectomy for healing or up to 6 months post chemotherapy. These delays allow clonogenic tumor cells to locally re-grow and potentially explain the risks of local failure. PDT delivered to the lumpectomy site immediately post lumpectomy or shortly thereafter may be a means to improve local control. Thus, PDT and whole breast radiation therapy may actually improve long-term local control over what is currently state of the art. It is important to emphasize that those patients undergoing chemotherapy will have whole breast radiation therapy delayed for several months likely increasing local failure rates. The use of PDT could minimize local failure. As this is a conservative approach to a new treatment intervention it may also have greater support among clinicians.

PDT as part of lumpectomy

As partial breast treatment is emerging as an option, PDT alone, taking a similar path to partial breast radiation, should be feasible. Currently, most partial breast radiation procedures take place days or weeks following lumpectomy to allow for final pathological analysis and evaluation of resection margins. PDT could be done using this paradigm. Potentially, an ideal model would involve a balloon that was inflated in the lumpectomy site with a centering catheter to allow for central placement of the illumination source. Thus, relatively homogeneous illumination to a spherical region could be accomplished. Also possible would be to place one or more illumination catheters into the lumpectomy bed. This could offer homogeneous illumination or modulation of the illumination to areas of increased risk (i.e. close margins) of local failure. Either method could employ ultrasound guidance to ensure optimal placement of the light sources relative to the surgical bed. It would not be difficult to assess response in the treated region by needle biopsy which could evaluate normal tissue as well.

PDT to intact tumors

Biopsy can offer significant data on histological characteristics of breast cancer so that gross tumor excision may not be necessary to ensure adequate pathological specimens. Particularly, very small lesions detected on mammography may not have adequate residual neoplasm for additional histology upon lumpectomy. With that in mind, radically PDT could be used to eliminate the tumor without resection. If PDT could destroy gross and microscopic disease then margin status may not be as important as it currently is with radiation therapy. Interstitial illumination fibers could be placed at the time of sentinel node evaluation and breast PDT as well as initial axillary evaluation could be accomplished in one sitting. As proof of principle, one might then excise the illuminated treatment bed either immediately or in a second sitting to truly evaluate the response to PDT. Histological analysis would reveal the true nature of treatment to both tumor and surrounding normal tissue. Conceptually, PDT could eliminate the lumpectomy and provide even better cosmesis. Further, whole breast radiation therapy could follow as well. Another potential venue would be to use PDT on large tumors that would currently not be candidates for breast conservation. If PDT downstages the mass and allowed successful resection this would be of tremendous value. This would also serve as a means to evaluate the effectiveness of PDT treatment in terms of depth of necrosis and normal tissue response.

Conclusions

Breast conservation and cosmetic concerns are playing a greater role in therapy. Surgery, radiation and systemic agents are being used in a much more precise fashion to minimize morbidity and maximize tumor control. PDT should be able to play a key role in enhancing tumor control and offering even better cosmesis then what is currently available. Further, PDT can be done under relatively primitive conditions and in a cost effective manner so that patients worldwide might have the opportunity to avoid mastectomy. Only well designed clinical trials will allow this to become reality.

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