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REVIEW

4 Photodynamic therapy for chest wall recurrence 5 from breast cancer

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KEYWORDS

Breast cancer;
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Chemotherapy

Summary

Breast cancer is common with over 230,000 new cases diagnosed each year in North America alone. While great strides have been made to achieve excellent cancer control and survival, a significant minority of patients fail locally. While initial salvage to regain disease control is of the utmost importance, it is not universally successful. This leads to a therapeutic quagmire. Additional surgery, radiation and chemo-hormonal therapy are possible, but they are usually highly morbid with low success rates. Photodynamic therapy appears to be an underutilized salvage modality for this unfortunate patient population. This report analyzes and reviews the role of photodynamic therapy for patients with chest wall re-recurrence from breast cancer.

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1 Introduction

2 Dramatic advances have occurred in the early de-
 3 tection and treatment of breast cancer. However,
 4 even with 90% or higher local control rates re-
 5 ported at 5-year follow up, a considerable num-
 6 ber of women still suffer local regional failure [1].
 7 Potentially, in North America alone, this translates
 8 to nearly 20,000 of the 230,000 new breast cancer
 9 cases diagnosed each year requiring salvage ther-
 10 apy for local-regional failure. Further, it is well doc-
 11 umented that local failure increases with longer
 12 follow-up. Eventually more than 15% of these pa-
 13 tients will require local salvage by 15 years post-
 14 treatment despite “curative” therapy [2].

15 Generally initial salvage for patients who fail
 16 breast-conserving therapy of lumpectomy and radi-
 17 ation is modified radical mastectomy [3]. For pa-
 18 tients who fail mastectomy full course radiation
 19 therapy is employed to the chest wall and regional
 20 lymphatics. Fortunately in both situations salvage
 21 therapy is generally successful with minimal acute
 22 morbidity for most patients. Salvage in these situ-
 23 ations usually incurs risk of arm edema as the most

common chronic side effect. Overall, several large
 series show that nearly 90% of patients undergo-
 ing salvage will regain local control [2,4–6]. For
 lumpectomy and radiation patients with isolated
 recurrence at the initial tumor site survival is nearly
 equivalent to similar patients who did not recur.
 Most patients who experience recurrence will un-
 dergo additional chemotherapy though no random-
 ized series exist to examine this important question
 and the benefit of this treatment.

Given the large number of patients diagnosed
 with breast cancer, the real risk of local failure,
 and the fact that local control from salvage does
 not approach 100%, a significant minority of breast
 cancer patients will re-recr loco-regionally. These
 individuals will most likely have already undergone
 one or more major surgical procedures for local
 control, full dose radiation and multi-agent chemo-
 hormonal therapy. Clearly, additional salvage op-
 tions with these modalities are limited. Photody-
 namic therapy (PDT) [7,8] has had considerable suc-
 cess in the treatment of cutaneous primary and
 metastatic malignant lesions and should be con-
 sidered for these unfortunate individuals. PDT has

48 the additional benefit of being a potentially pain- 98
49 less outpatient procedure that is repeatable. PDT 99
50 can work in combination with other salvage regi- 100
51 mens or as a stand-alone therapy. In a simplistic 101
52 overview, PDT has three main components: first a 102
53 sensitizing agent, which preferentially accumulates 103
54 in malignant/pre-malignant tissues and/or clears 104
55 faster from surrounding normal tissue; second, a 105
56 source of intense illumination, which at the ap- 106
57 propriate wavelength will activate the sensitizer. 107
58 This leads to the third component of PDT, oxy- 108
59 gen, which in the course of the photodynamic re- 109
60 action is transformed into singlet oxygen. The gen- 110
61 eration of singlet oxygen allows for the rapid cy- 111
62 toxic/vasculotoxic activity associated with PDT. We 112
63 will analyze and review the PDT literature, based 113
64 on published peer reviewed papers, concerning this 114
65 important patient population. 115

66 Natural history of chest wall lesions

67 Once tumor cells have invaded dermal lymphatics, 116
68 they appear free to travel extensively in this cuta- 117
69 neous system [9]. As these lymphatics are without 118
70 direction, due to lack of valves, metastasis originat- 119
71 ing from the chest wall can spread to the contra- 120
72 lateral chest, abdomen and even the back. This ex- 121
73 tensive spread explains the virtual complete failure 122
74 of nidusectomy, attempted at what appears to be 123
75 a solitary metastasis. As these lesions grow, they 124
76 often cause intensive signs and symptoms. Com- 125
77 monly, patients report an unrelenting itching which 126
78 is not relieved by topical steroids or shots. Many 127
79 patients report pain from these lesions as well as mo- 128
80 tion limitation due to discomfort. Eventually, the 129
81 lesions begin to weep and bleed causing further dis- 130
82 tress. Open tumor infiltrated wounds and infections 131
83 that are poorly controlled follow. Lesions may im- 132
84 pinge on the brachial plexus and remaining axillary 133
85 nodes leading to additional neurologic difficulties 134
86 and edema. The quality of life for these individuals 135
87 and their caretakers can become poor. As lesions 136
88 progress uncontrollably, psychological and physio- 137
89 logical distress occurs as might be expected from 138
90 individuals watching their cancers grow in front of 139
91 their eyes. Some patients will succumb due to the 140
92 combination of infected wound, pain and tumor 141
93 burden [10,11]. 142

94 Salvage for re-recurrence: options

95 Surgery

96 With the extensive dermal lymphatic involvement 143
97 of the skin, a local approach to excision virtually 144
145
146
147
148
149
150
151

always fails [9]. As it is impossible in many pa- 98
tients to obtain clear margins, which would allow 99
for wound healing, further surgery must be ap- 100
proached cautiously. Even highly selected patients 101
who have been deemed candidates for chest wall 102
resection often followed by additional radiation and 103
chemotherapy generally fail at the margins of re- 104
section [12,13]. Further, these patients have fairly 105
high morbidity even in the best surgical hands [14]. 106
It would be clinically more efficacious to excise and 107
close wounds in a sterilized field than to leave a tu- 108
mor infested wound and expect healing. Should the 109
tumor bed be sterilized, for example by PDT, a va- 110
riety of plastic surgery grafts could be employed 111
to close defects, if needed. In this situation, as 112
no viable tumor would prevent healing, potentially 113
one could expect excellent clinical and cosmetic 114
effects. 115

Radiation

Radiation is a highly effective modality for patients 116
with initial recurrence post-surgery [15,16]. Ra- 117
diation has the benefit of treating the recurrent 118
field and regional lymphatics with excellent clini- 119
cal and cosmetic outcomes [17]. Patients with re- 120
currence post-radiation are extremely difficult to 121
re-irradiate. This is due to the well-established tol- 122
erances of tissue to radiation. After a first course of 123
radiation therapy, the lung, soft tissue, ribs, lym- 124
phatics and nerves in the prior radiation field are 125
near tolerance levels. An additional course of ra- 126
diation to recurrent disease will likely bring these 127
critical normal structures beyond tolerance. This 128
can have severe clinical complications in terms 129
of symptomatic pneumonitis, arm edema, plex- 130
opathies, fibrosis and wound healing difficulties 131
[18–20]. 132
133

Chemo-hormonal therapy

Re-recurrent lesions often bode for systemic fail- 134
ure. Most patients should undergo additional stag- 135
ing for extent of disease work-up. This includes 136
chest, abdomen, pelvic CT and bone scan. Tu- 137
mor markers may be of benefit. Patients with 138
widespread and progressing systemic disease may 139
not need local treatment in as urgent a fash- 140
ion as they need systemic therapy. Most patients 141
who have chest wall re-recurrence have already 142
failed primary and salvage chemo-hormonal treat- 143
ment [21–23]. Many have failed additional salvage 144
courses of chemotherapy as well. It is rare for 145
third-line treatments to effectively control chest 146
wall failure for any prolonged period. Further, no 147
clear data exists that correlates systemic response 148
with chest wall response for these patients. Even 149
in the face of systemic improvement, local re- 150
151

control can be poor. This may be due to the poor hematologic delivery of chemotherapeutic agents to the chest wall as its blood supply may be compromised due to surgery and radiation, most likely on several occasions. It is recognized that certain chemotherapy agents are potentially radiation sensitizers and perhaps PDT sensitizers. This may complicate the treatment of chest wall disease. It may also increase normal tissue morbidity [24].

PDT

As currently practiced, PDT involves a photosensitizing agent that is activated optimally by a particular wavelength of light [7,25–27]. Ideally this results in a photodynamic reaction. The reaction creates highly cytotoxic and vascular toxic free radicals leading to tumor cell death and immuno-modulation. As PDT has been employed to a wide variety of cutaneous neoplasms with excellent clinical and cosmetic outcome, it is reasonable to hypothesize that chest wall lesions would be amenable to this therapy. As PDT works well even in operated upon and radiated fields, this would be a means for additional salvage options. We will review the treatment and outcome results in the published literature for each photosensitizer.

PDT for chest wall recurrence/ re-recurrence from breast cancer

Photosensitizers

Photosensitizers are substances that transfer and translate light energy into a type II photodynamic reaction [28]. The oxygen-based reaction creates toxic singlet oxygen species for tumor ablation. Photosensitizers may be natural or synthetic. In general the three main families for photosensitization are porphyrin based, chlorophyll based or dye based [29–33]. The porphyrins are ring structures. Those tried in breast cancer treatment included hematoporphrin derivatives (HPD; Photofrin®), aminolevulinic acid (ALA) – a prodrug which stimulates the production of the naturally occurring photosensitizer Protoporphyrin IX (PPIX) – and the synthetic porphyrin TPPS4. An open ring porphyrin based texaphyrin, Lutex, has also been examined. Chlorophyll based compounds have also been explored including Foscan® (MTHPC) and HPPH, which are chlorines and Purlytin (SnET₂), a purpurin, which is a degradation product of chlorin. As yet, no dye has been tested

for this indication and reported in peer reviewed literature.

Illumination

Appropriate illumination should allow for activation of the photosensitizer. The longer the wavelength of light, the deeper the penetration into and through the skin. As most chest wall lesions can approach 1cm or more in depth, one generally will require an activation wavelength to readily penetrate this deep. Photofrin® and ALA/PPIX activate around 630 nm. This allows for at least 1 cm light penetration and should be adequate for most situations. ALA has a lesser penetration depth because it is applied locally, and the drug only diffuses to a few mm depth. Deeper lesions may require interstitial therapy; however, even lesions approaching 2 cm were successfully treated by superficial means using Photofrin® [25,34,35]. Purlytin's (660nm) and Foscan®'s (652 nm) should behave similarly to Photofrin® in depth penetration. Lutex with 732 nm treatment wavelength may have deeper penetration. Illumination to activate the photosensitizers can be by multi-wavelength light or more efficiently by monochromatic light at the appropriate wavelength. This can be generated by intense white light with filters or more accurately by laser light at the specific wavelength. Light is transmitted from the source (i.e. laser) by fiberoptics for illumination. The illumination may be done using a diffusing fiber for multi-directional illumination, which is good for interstitial and intraluminal work, or a micro lens, which like a flashlight projects in a single forward direction. Many other types of fibers also exist. All lesions are more selectively activated by using a micro lens aimed at the treatment field. This will illuminate in circular field, and appropriate light blocking can be added. By blocking light from surrounding or reflected surfaces, one will minimize normal tissue toxicity. Inappropriate blocking of light may block illumination of tumor. One should avoid light field junctions over tumor beds to minimize light inhomogeneity due to gap or overlap of the light fields. This could allow for under-dosage in the tumor bed and treatment failure. Overlapping light fields can allow for over light dosage and severe morbidity, particularly to normal tissue. Light emitting diodes can also be used as a substitute for the laser in the treatment of superficial lesions. Its advantage is that they can be manufactured to treat a large area in one setting, making the treatment shorter and more comfortable to the patient. The efficacy of the LED as a replacement for a laser has been studied by Ferreira et

256 al. (Lasers Med Sci 2004, submitted for publica-
257 tion).

258 PDT reaction

259 While it has been demonstrated that most photo-
260 sensitizers induce PDT by a photodynamic reaction,
261 the location of this reaction may be of clinical con-
262 sequence. Photofrin[®] accumulates at the outer cell
263 membrane and upon activation may induce apopto-
264 sis as well as cell death by cell membrane destruc-
265 tion. This may then lead to cytokine release and
266 immune system activation. Clearly this may bene-
267 fit patients with systemic disease. Other sensitizers
268 are more selective in their location of concentra-
269 tion and may cause mitochondrial destruction lead-
270 ing to apoptosis without systemic immune activa-
271 tion since they don't destroy the cell membrane
272 leading to cytokine release. This may well avoid
273 immune stimulation and have clinical ramifications
274 [36].

275 Dosimetry

276 Ideally real time dosimetry would exist to assist
277 in therapy. Accurate dosimetry would allow opti-
278 mization for an appropriate light dose to destroy
279 malignancy with minimal or no normal tissue dam-
280 age. Optimally, the dosimetry system would in-
281 form the user that adequate treatment had been
282 delivered. No such system exists today, although
283 progress have been reported on photosensitizer
284 photobleaching (see photobleaching section below)
285 and other PDT effects as an indication of treat-
286 ment efficacy. Therefore therapeutic decisions are
287 made with the rather empirical use of drug and light
288 dose. This would explain why some treatments are
289 more successful than others based mainly on clin-
290 ical skill and judgment rather than accurate infor-
291 mation. Until accurate dosimetry is available, clini-
292 cians will need to be highly cautious when using ex-
293 tremely active sensitizers or, when high concentra-
294 tions of less active sensitizers are employed. Low-
295 dose Photofrin[®] can be successful even when part of
296 the treatment field is illuminated twice (e.g. field
297 junctions). Low-dose Photofrin[®] is very forgiving in
298 these situations due likely to photobleaching (see
299 below).

300 Fluorescence

301 A major issue in any treatment is where the tar-
302 get is located. Clearly symptomatic lesions are easy
303 to identify and response to PDT can be accurately
304 gauged both clinically and by biopsy. Less clear are

subtle lesions and areas at risk. In these cases, 305
clinical experience is required. It would be better 306
to have a reproducible ability to detect and de- 307
fine treatment fields [37–39] as well as response 308
[40–43]. It is here that most photosensitizers can 309
shine as most photosensitizers also fluoresce. By vi- 310
sual means or by more sophisticated techniques, it 311
is hoped that fluorescence can be used to better de- 312
fine treatment fields and outcome. This is an area 313
of active research, but results are preliminary. The- 314
oretically the change in fluorescence could also be 315
used as a real time dosimeter. Potentially, sensitiz- 316
ers that fluoresce could be used to optically biopsy 317
lesions [44–53], treat them, dose them appropri- 318
ately and define a successful therapy without bias. 319

320 Photobleaching

321 Clinically, one can exploit photobleaching to en- 321
hance tumor response and minimize normal tissue 322
toxicity [34,54]. Higher photosensitizer drug dose 323
appears to minimize selectivity in PDT response be- 324
tween tumor tissue and normal tissue [55]. This may 325
be explained by photobleaching kinetics. In clinical 326
photobleaching, as little photosensitizer as possible 327
is employed to destroy tumor. Since sensitizers con- 328
centrate to a certain degree higher in tumor than 329
normal tissue then one should have more PDT in 330
tumor. Using as little sensitizer as possible spares 331
normal tissue by minimizing PDT at that location. 332
If more sensitizer is infused than needed, more will 333
go to both tumor and normal tissue. Even though 334
more sensitizer is still in tumor than normal tissue 335
enough sensitizer is still in normal tissue to create 336
significant PDT. Therefore, by infusing as little sen- 337
sitizer as is needed to destroy tumor beds one can 338
minimize normal tissue toxicity and enhance selec- 339
tivity by photobleaching. 340

341 Reported outcomes from clinical trials

342 Photofrin[®]

343 Photofrin[®], a hematoporphyrin derivative, is a 343
member of the porphyrin family which has been 344
employed in a number of trials [34,56–65]. In ad- 345
dition to highly variable drug dose, light dose and 346
drug to light interval time, dissimilar patient pop- 347
ulations also appear to exist. Complicating mat- 348
ters even more, the reporting of response varies 349
from series to series, sometimes including lesions 350
response rates, patient response, and volume re- 351
sponse among others. These varying endpoints of 352
analysis and treatment techniques make it difficult 353

354 to compare the published data. As Photofrin[®] has
355 the longest history of availability, it is not surpris-
356 ing that this photosensitizer has the most clinical
357 reporting. Many of the early works included drug
358 dose, light dose and drug to light interval time vari-
359 ations which are, based on today's 20–20 hindsight,
360 clearly inadequate. However, each series added to
361 our knowledge, and taken as a whole, truly give us
362 impressive insight into appropriate therapy.

363 Photofrin[®] (HPD) has been infused from
364 0.6 mg/kg to 4 mg/kg for breast patients. Illumina-
365 tion has ranged from 20 to 360 J/cm². Generally,
366 drug to light interval was about 48 h, but could
367 range to 1 week. Complicating matters further is
368 that current micro lens construction appears more
369 amenable to therapy than older fibers and may of-
370 fer more homogeneous illumination. Despite all of
371 this, complete response rates of 100% with minimal
372 morbidity is possible. It is also possible to overdose
373 normal tissue with drug or light and induce serious
374 morbidities. These morbidities to normal tissue can
375 present with pain, fibrosis, scarring and altered
376 pigmentation causing serious cosmetic concerns
377 among others. Since most patients treated for
378 chest wall recurrence have tissues injured by prior
379 salvage, healing is of great concern. That is why it
380 is appropriate to analyze data to reveal which tech-
381 niques offer the best response with least morbidity.

382 In an elegant series from Roswell Park, infusions
383 of Photofrin[®] from 0.57 to 2.5 mg/kg with illumi-
384 nation from 30–350 J/cm² at 48 h were reported
385 [57,58]. Minimal response at 0.57 mg/kg even with
386 244 J/cm² light was seen. This shows a minimum
387 threshold for response. Further patients infused at
388 2 mg/kg had much higher treatment related mor-
389 bidity than patients infused with 1 mg/kg. Partic-
390 ularly, individuals infused at 2 mg/kg illuminated
391 with light doses greater than 72 J/cm² were at
392 greatest risk. Interestingly 6 patients infused at
393 0.75 mg/kg and illuminated at 140–182 J/cm² had
394 excellent response with minimal normal tissue tox-
395 icity. Similar response was also seen in patients
396 with high light and drug dose, but morbidity in
397 those patients was much more severe. This we feel
398 demonstrates a drug and light dose that not only
399 was threshold for breast PDT but likely exploited
400 photobleaching to minimize normal tissue toxic-
401 ity. Since Photofrin[®] for breast metastasis accu-
402 mulates a bit more in malignancy than normal tis-
403 sue, the 0.8 mg/kg allows for tumor destruction,
404 but the 0.8 mg/kg is not enough to allow for sig-
405 nificant PDT in surrounding normal tissue. Due to
406 normal tissue morbidity found at 2 mg/kg, illumi-
407 nation fields in the Roswell Park report were very
408 tight around lesions. This led to many patients ex-
409 perencing recurrence at the rim of the illumination

field which would require additional salvage treat- 410
ment. Patients treated at 0.8 mg/kg on this series 411
also had very tight light fields leading to rim recur- 412
rence. 413

414 Based on photobleaching and the concept that
415 0.8 mg/kg with 150 J/cm² were near optimal for tu-
416 mor control with minimal morbidity larger illumina-
417 tion fields were employed in a more recent publi-
418 cation [34]. Here margins well beyond the tumor
419 nodule at risk were illuminated. Rim recurrence
420 was not generally seen and virtually all lesions were
421 eliminated. Overall, it appears that 98% of the time
422 chest wall lesions could be stopped from growing or
423 eliminated. Despite all patients having undergone
424 extensive surgery, high dose radiation and multiple
425 chemo-hormonal therapies, cosmetics was judged
426 to be excellent. Using the same parameters, the
427 East Carolina University (ECU) experience was re-
428 cently published [61]. Patients, including those with
429 large confluent lesions, who had failed all salvage
430 including radiation were illuminated with wide mar-
431 gins. Drug dose was 0.8 mg/kg with illumination at
432 48 h by 630 nm light at 150 J/cm². All lesions re-
433 sponded and 9 of 14 patients had total elimina-
434 tion of chest wall disease. Five of 14 patients had
435 most lesions cleared, but remained with some ar-
436 eas of non-growing tumors and were called par-
437 tial responders. Overall out of 500 lesions treated,
438 more than 90% were complete response. As all pa-
439 tients were followed closely, it became apparent
440 that even wider margins of illumination are needed
441 in patients with chest wall metastasis. Several pa-
442 tients failed beyond the edge of the illumination
443 field which generally already included 2 cm margin.
444 With the drug/light dose employed larger margins
445 of illumination were possible without additional
446 normal tissue toxicity. Perhaps larger margins will
447 be required to be illuminated to further increase
448 control rates. High response rates have also been
449 reported with 2–3 mg/kg of Photofrin[®] and light
450 doses of 100 J/cm² [60]. Of note, however, is the
451 significantly higher morbidity seen including wound
452 healing difficulties, fibrosis and treatment related
453 pain. These drug/light doses also do not seem to
454 offer the selectivity in PDT between normal and
455 tumor tissue requiring tight illumination borders.
456 This would also increase the chance of rim recur-
457 rence. Other authors [57,62] have also reported
458 high normal tissue toxicity with high drug and/or
459 light doses, again pointing the way toward lower
460 drug concentrations for these particular patients.
461 Chemotherapy agents may interact synergistically
462 with PDT to potentially enhance response of tu-
463 mors, however, normal tissues maybe sensitized as
464 well leading to enhanced toxicity of normal tissues
465 [24]. The net result may not be of clinical benefit. 466

466 While many different Photofrin[®] drug/light dose
467 schedules can offer high tumor response, normal
468 tissue toxicity can be significant. Further, as der-
469 mal invasion leads to widespread disease, wide bor-
470 ders of illumination to seemingly normal appearing
471 but tumor-containing tissue is needed. By exploit-
472 ing photobleaching, low-dose Photofrin[®] appears to
473 offer excellent tumor response with minimal normal
474 tissue toxicity. Even heavily operated upon and
475 irradiated fields respond well. Low-dose Photofrin[®]
476 PDT has also allowed for surgical graft placement
477 in a wound defect in the center of a field sterilized
478 by PDT [61]. This clearly offers select patients even
479 more opportunity for salvage.

480 For patients treated with Photofrin[®], the actual
481 illumination procedure appears relatively painless.
482 Some series report a slight stinging towards the
483 end of each field illumination. Most patients have
484 minimal post-PDT related pain as well. Overall, it
485 appears to be a well tolerated procedure. When
486 2 mg/kg of Photofrin[®] is used, patients must main-
487 tain direct sunlight precautions for a minimum of
488 4 weeks. At doses of 0.8 mg sunlight sensitization
489 appears rare at 4 weeks.

490 Lutetium texaphyrin

491 Lutetium Texaphyrin (Lu-TeX), a member of the
492 texaphyrin family of sensitizers [66], has also been
493 examined in patients with locally recurrent breast
494 cancer [66–68]. Patients who failed salvage, in-
495 cluding radiation therapy, were infused with vary-
496 ing drug doses of 0.6–7.2 mg/kg, 3–96 h prior
497 to illumination. Illumination at 732 nm generally
498 at 150 J/cm² was then employed. At dose above
499 5.5 mg/kg, treatment could not be completed due
500 to pain during illumination. Dysesthesia in light ex-
501 posed areas also occurred. A 27% CR was reported.
502 Additional patients were treated with 1–3 mg/kg.
503 Most patients experienced pain at the treatment
504 site during therapy. Response rates were marginally
505 better. As part of this study dosimetry was exam-
506 ined for patients infused with either 4 or 5 mg/kg
507 and illuminated with 150 J/cm². Interestingly flu-
508 ence rates varied by up to 70% in the treatment
509 field, which may have contributed to the limited
510 CR rates as well as morbidity [69]. This study also
511 revealed that treatment 3-h post-infusion is asso-
512 ciated with minimal selectivity and excess toxicity
513 while treatment beyond 24 h was without photo ac-
514 tivity.

515 Npe6

516 In a phase I study of the chlorin, mono-l-aspartyl
517 chlorin e6 (Npe6), Taber et al. [70] reported on

518 patients with recurrent chest wall lesions who
519 failed prior salvage. In this dose–light finding study
520 0.5–3.5 mg/kg of Npe6 were intravenously applied
521 to the patients. Approximately 4 h later, lesions
522 were illuminated from 25 to 100 J/cm² at 662 nm.
523 Tumor regression and eschar formation was always
524 noted, but patients always failed within this treat-
525 ment field at doses of drug \leq 1.65 mg/kg. Patients
526 infused with 2.5 or 3.5 mg/kg and illuminated at
527 100 J/cm² allowed for 66% complete remission (CR)
528 rate. However, at drug dose of 2.5 mg or above no
529 normal tissue selectivity was seen in the treatment
530 fields. While the PDT treatment was tolerated all
531 patients were photosensitive for 2 weeks.

532 MTHPC

533 Another chlorin family member, MTHPC, Foscan[®]
534 has also been evaluated [71,72]. A total of 7 pa-
535 tients with chest wall recurrence underwent PDT
536 in 11 sessions. Most patients had failed radiation,
537 but some did not undergo radiation salvage post-
538 mastectomy. Three patients underwent 0.1 mg/kg
539 infusion followed by illumination at 48 h at 5 J/cm².
540 Eight treatments on five patients occurred follow-
541 ing 0.15 mg/kg infusion with illumination at 96 h at
542 10 J/cm². All illumination was at 652 nm. Normal
543 tissue was covered by plaster with a hole cut out for
544 the illumination field. Six of seven patients had PDT
545 related pain. This pain generally lasted for 2 weeks
546 post-treatment. Narcotic analgesia was needed for
547 several patients. One patient, who had undergone
548 prior radiation treatment, had extreme pain devel-
549 oped within her radiation field. Another patient suf-
550 fered photosensitivity from a reading light. While
551 all 89 lesions appeared to have CR it is interesting to
552 note that 4 of 7 patients needed additional PDT due
553 to recurrences bordering the prior PDT fields. This
554 rim like recurrence appears to be due to the nor-
555 mal tissue toxicity noted in the illuminated fields
556 requiring the physicians to treat as small a skin vol-
557 ume as possible. The authors report areas greater
558 than 12 cm² to cause delayed slough off of necrotic
559 tissue. Tissue healing time for areas treated greater
560 than 12 cm² was greater than 3 months. While ob-
561 viously a very potent and successful treatment for
562 chest wall patients the optimal use of this pho-
563 tosensitizer for this indication is far from known.
564 The very limited treatment fields possible with the
565 drug–light doses used clearly allowed for failure in
566 skin bordering illumination fields. This is not unlike
567 some of the earlier reports on Photofrin[®], where
568 drug/light dose combinations were employed and
569 were not optimized. Patients were also sunlight and
570 dark light sensitive for 2 weeks post-infusion. This
571 may have more quality of life limitations than 4

572 weeks of sunlight photosensitivity from low-dose
573 Photofrin®.

574 Purlytin

575 Purpurins, derivatives of chlorines also have been
576 tested. Purlytin, tin ethyl etiopurpurin, was exam-
577 ined on eight patients who had failed conventional
578 salvage regimens including radiation [73]. The drug
579 was infused at 1.2 mg/kg and illumination was un-
580 dertaken 24 h later at 660 nm with 200 J/cm² via
581 micro lens. A complete response rate of 92% with
582 partial response rate of 8% was reported. No pa-
583 tient had lesion re-growth within the illumination
584 fields and cosmetic results were excellent. Good
585 wound healing without fibrosis was noted. Therapy
586 was always as outpatient and with minimal discom-
587 fort. Good selectivity was noted within illumina-
588 tion field. Margins of illumination of at least 1 cm
589 were used. No rim recurrences at the borders of
590 the illuminated fields were seen. No sunlight pho-
591 tosensitization was reported and sunlight precau-
592 tions were employed for 2 weeks post-infusion. Simi-
593 lar good outcomes were published in case report
594 form [74].

595 ALA/PPIX

596 ALA, 5-aminolaevulinic acid is a pro-drug [75,76].
597 Introduction of ALA overloads the heme synthetic
598 pathway and lead to excess Protoporphyrin IX, an
599 active photosensitizer. This member of the por-
600 phyrin family activates around 630 nm and has had
601 excellent response on superficial malignant and
602 pre-malignant skin lesions. However, ALA is gen-
603 erally applied as a superficial cream, which while
604 greatly convenient, is sub-optimal for nodular le-
605 sion therapy. The wavelength of light should al-
606 low for deep enough tissue penetration, but the
607 cream itself must not be able to diffuse far enough.
608 Even when introduced systemically (orally or intra-
609 venous) ALA/PPIX has limited depth penetration. It
610 also loses a significant amount of tumor versus nor-
611 mal tissue selectivity as compared to topical appli-
612 cation. This would explain the very poor response
613 rates for breast metastasis, which are usually nodu-
614 lar [77]. Conceivably ALA could be used via a multi-
615 visit regimen of repeated topical applications and
616 illumination, but would lose its convenience. It is
617 also quite a painful therapy.

618 TPPS4

619 A substituted porphyrin, meso-tetra para sulpho-
620 phenyl porphin (TPPS4) has also been used for

chest wall recurrence [78,79]. This drug was
found to be neurotoxic on systemic application.
An alternate use has been by intra-lesional injec-
tion, without the reported neurotoxicity. In 9 pa-
tients who failed initial salvage, including radi-
ation, TPPS4 was introduced into each lesion at
0.15 mg or 0.3 mg via injection. Illumination began
45 min later at 630 nm with fluence of 150 J/cm².
Only 33% CR rates were reported with follow-
up of 6–8 months. Of note, most lesions re-
quired an average of 12 injections/illuminations
to achieve this result. Clearly, this is not a
very convenient treatment regimen for patient or
caregiver.

Summary of trials

The results and parameters of the clinical studies
used in chest wall PDT are outlined in Table 1 for
Photofrin® and other photosensitizers. PDT is ac-
tive and potentially has an excellent outcome as a
salvage tool even in heavily pretreated tissue. The
drug can accumulate in tissue damaged by surgery,
radiation and chemotherapy. Even with illumina-
tion lethal enough to destroy tumors, normal tissue
can heal without intervention. Particularly note-
worthy is that the healed skin is not fibrotic, and
has excellent cosmetic results. It is also very clear
that Photofrin®, with its long clinical history, and
its published data for this population of patients,
can be clinically successful with minimal morbidity.
While many drug/light doses can bring success,
some appear to have higher side effects. Our expe-
rience shows that low-dose Photofrin® at 0.8 mg/kg
and illumination at 150 J/cm² gives a reliable and
excellent outcome.

Other sensitizers are also able to offer good
response, but the patient population so far ex-
amined is small and follow-up is short. Many of
these sensitizers are not always commercially avail-
able and appropriate wavelength light sources
may not be available either. Clearly, the po-
tential for these photosensitizers to outperform
Photofrin® is possible, but has not yet been reli-
ably shown. Only larger multi-institutional clinical
trials will be able to ascertain this type of infor-
mation.

One also should be cautious about the pa-
tient population examined. Most of the published
literature was for patients with recurrent chest
wall disease. However, some studies included a
re-recurrent patient population. These individu-
als have undergone multiple surgeries, radiation
courses, and chemotherapies. They are more likely
susceptible to normal tissue morbidity but excel-
lent results are still possible [34,61].

Table 1 Clinical Studies for Chest Wall PDT

Drug	Number of patients	Number of fields	Number of Tx sessions per patient	Drug dose (mg/kg)	Wavelength (nm)	Fluence (J/cm ²)	DTI ^a (h)	CR ^b (%)	PR ^c (%)	MR ^d (%)	Morbidity ^e (%)	Photosensitivity patients	Follow-up months	Reference
Photofrin®	14	500	1	0.8	630	150	48	91*	7	2	7	0	>6	[61]
Photofrin®	9	102	1	0.8	630	150	48	89	8	3	0	0	>6	[34]
Photofrin®	4	4	1	0.57	630	30–244	48	0	0	0	0	0	>6	[57,58]
	6	6	1	0.75	630	140–180	48	66	16	16	0	0	>6	
	27	NR	1–6	1–2.5	630	36–288	48–120	19	48	33	50	2	>6	
Photofrin®	7	11	1–3	1–2	630	<100	48	0	20	0	0	1	>6	[60]
Photofrin®	14	33	1–4	1.5**	630	<50	48, 72, 96	14	42	42	50	0	>6	[59]
	6	47	1–4	1.5	630	≥50	48, 72, 96	0.33	50	16	50	0	>6	
Photofrin®	15	NR	1	2–3	630	25–200	48	20	80	0	50	0	>6	[62]
Lutex	16	16	1	0.6–7.2	732	150	3–96 h	27	33	37	50	0	3	[68,69]
	25	38	2	1–3	732	150	3 h	47	29	24	25	1	3	
Npe6	3	3	1	1.65	664	25–100	4 h	0	0	0	0	0	3	[70]
	8	11	1	2.5–3.5	664	100	4 h	66	0	33	100	0	3	
MTHPC	7	89	1 or 2	0.1–0.15	652	5–10	48–96 h	100	0	0	100	1	4	[72]
Purlytin	8	86	1	1.2	660	200	24 h	92	8	0	15	0	>6	[73]
ALA	5	14	1	20%	630	150	4 h	35***	0	35****	30	0	6	[77]
TPPS4	9	NR	12	0.15–0.30	630	150	1 h	33	22	44	0	0	6	[79]

^a Drug infusion to light illumination interval.

^b Complete response.

^c Partial response >50%.

^d Minimal response.

^e Morbidity for Photofrin® includes: severe Tx pain, wound healing problems, scar; morbidity for other drugs includes: severe Tx pain, wound healing problems, scar, normal tissue injury (or or more of each).

* 91% (465/511 lesions); 9/14 patients with CR, 5/14 with PR.

** Highly active version of photofrin, potentially equivalent to 3 mg/kg.

*** Isolated nodules <1 cm.

**** Minimal response to nodules >1 cm.

674 Treatment techniques

675 Patient positioning

676 Unlike many patients who undergo PDT, patients
 677 with chest wall disease pose certain unique con-
 678 siderations. First and foremost patients generally
 679 have numerous lesions requiring therapy. Since ide-
 680 ally each lesion should be treated appropriately,
 681 a system of identifying the lesion and ensuring it
 682 is illuminated is essential. As some individuals will
 683 have 50 treatment fields, memory will not suffice.
 684 We recommend an anatomical drawing to be used
 685 in conjunction with patient coordinates and land-
 686 marks. The suprasternal notch and tip of xyphoid
 687 process are easily defined and can serve as refer-
 688 ence, as can the clavicle. Surface marking by ink at
 689 even intervals can assist. This grid will allow for sys-
 690 tematic rather than haphazard treatment and avoid
 691 geographic misses as well as treatment of the same
 692 anatomy twice by mistake. Additionally, patients
 693 who have numerous lesions will require comfort-
 694 able positioning to minimize movement during illu-
 695 mination. Since chest wall PDT is accomplished in a
 696 fully conscious outpatient setting we recommend a
 697 very comfortable treatment couch or bed. Follow-
 698 ing along these lines, setting up for illumination is
 699 time consuming so making the most efficient use
 700 of the micro lens set-up is important. Stands that
 701 allow for easy adjustment of the light are needed.
 702 Mobile stands that can be rapidly moved and locked
 703 into place for the next illumination are very im-
 704 portant. Critically, patients who have widespread
 705 lesions may need to be turned over or around to
 706 reach treatment sites. As PDT can give rapid ther-
 707 apeutic outcome with treatment lesions becoming
 708 very tender or weeping, one must use considerable
 709 forethought deciding which lesions will be treated
 710 first and which last. One does not want to treat
 711 the asymptomatic lesions, cause them to become
 712 tender, and thus prevent treatment of symptomatic
 713 anatomy. With patients requiring multiple planes of
 714 illumination and multiple anatomical regions (i.e.
 715 chest wall, abdomen, shoulder, etc.) considerable
 716 treatment planning must be done prior to patient
 717 positioning, otherwise therapy will not be able to
 718 be completed.

719 Illumination

720 As critical as patient positioning, and deciding
 721 which anatomical region is to be treated in which
 722 sequence, is the ability to deliver homogeneous il-
 723 lumination. It is important that the light source be
 724 incident to the anatomy, otherwise over and under

light dosage could occur in each field. Further, the
 light sources must be able to reach each anatomi-
 cal area, thus light source mobility and location is
 part and parcel of patient set-up. Since it is im-
 portant not to overlap light fields (i.e. over illu-
 minate) it is critical that accurate placement of
 fibers be maintained throughout therapy. As patient
 anatomy varies dramatically it is easy to over and
 under dose. Further, patients may move during il-
 lumination and a means to re-position patient/and
 or light in real time is critical. It is also critical that
 illumination fields not cut through or partially illu-
 minate tumor beds for this will potentially under
 dose lesions. As palpable lesions only represent the
 tip of the iceberg, it is also critical that generous il-
 lumination margins around disease be used. In con-
 sideration of the added uncertainty of patient mo-
 tion, we suggest at least 2 cm margin. If indicated,
 following illumination, an ice patch applied to the
 treatment fields while the next treatment field is
 being illuminated will usually eliminate any acute
 treatment related pain.

The indications for interstitial illumination are
 unclear as the majority of reports employ only sur-
 face illumination. Even lesions approaching 2 cm
 depth can be successfully treated with surface il-
 lumination when Photofrin® is employed. Photo-
 sensitizers such as Foscan and Lutex theoretically
 can treat even thicker lesions from the surface. In
 general interstitial implants are done for bulky le-
 sions greater than 2 cm in depth. The implanted il-
 lumination source is usually placed at the base of
 the lesion, close to the skin to ensure deep light
 penetration. Implanted fibers should be about 1 cm
 apart. The use of small amounts of local anesthetic
 may help to ease placement pain. Some anesthetics
 can impede blood flow, which may alter photosen-
 sitizer concentration. Bleeding may absorb treat-
 ment light.

Specific precautions

Photosensitivity

All sensitizers will offer sunlight photosensitivity
 [28]. For Photofrin® at 2 mg/kg, 4–8 weeks of
 precautions are needed. At 0.8 mg/kg we have
 found sunlight photosensitivity rare after 4 weeks.
 Purlytin patients were sensitive for 2 weeks [73]
 and Foscan® [72] patient to 10 days. In general,
 sunlight precautions apply only to sunlight or simi-
 lar intense light. Patient's skin must be covered and
 wrap around sunglasses as well as a wide brim hat
 is recommended. Reflected light, for example from

776 a car window, can cause photosensitivity reaction.
777 In general, room light is safe. Foscan[®] patients may
778 be sensitive even at minimal light levels and reports
779 exist of toxicity occurring from sitting near a light
780 bulb or fireplace. As most patients with chest wall
781 recurrence have undergone multiple surgeries, ra-
782 diation and chemotherapies, they are well versed
783 in toxicity. We have found in our practice, that the
784 sunlight precautions have not prevented any pa-
785 tient from signing informed consent for therapy.
786 However, if you encounter a patient unable to, or
787 unwilling to accept this precaution, they should not
788 be readily offered PDT.

789 Illumination

790 Depending on the photosensitizer and its treatment
791 parameters, morbidity to normal tissue during illu-
792 mination is possible. Foscan[®] patients must have
793 non-illuminated regions heavily blocked from scat-
794 ter of light [72]. As this drug is so active, scattered
795 light is often enough to initiate PDT. While employ-
796 ing Foscan[®], one must use significant effort to en-
797 sure no scatter to tissue you do not wish to treat.
798 It is also very important to not overlap illumination
799 fields as tissue necrosis may occur. Similarly, when
800 2 mg/kg of Photofrin[®] is employed one also must be
801 extremely careful concerning illumination overlap
802 to prevent serious morbidity. Interestingly, likely
803 due to photobleaching, when low-dose Photofrin[®]
804 (0.8 mg/kg) is employed, no additional morbidity is
805 clinically noted during illumination overlap. Indeed
806 as micro lens illumination is circular and few tumor
807 beds are circular, the ability to overlap illumination
808 fields without undue morbidity is the great advan-
809 tage to low-dose Photofrin[®].

810 Pain control

811 Depending on the sensitizers and treatment vari-
812 ables, pain may or may not occur during therapy.
813 With ALA and Foscan[®] illumination all patients ex-
814 perience pain [31,75]; this is rare with low-dose
815 Photofrin[®]. In cases where pain occur an ice patch
816 to the affected area generally works. Numbing the
817 skin prior to therapy has been tried, but failed.
818 We suggest patients be dispensed narcotic or non-
819 narcotic pain pills prior to illumination to minimize
820 treatment difficulties.

821 Many patients have painful chest wall lesions
822 that impact on their quality of life. PDT is often
823 able to offer pain control via successful therapy. De-
824 pending on the photosensitizer and treatment pa-
825 rameters, the actual PDT can be painless or painful.
826 In general excellent pain control from lesion dimin-

ishment can be seen within 2 weeks of the PDT
session. During this time, however, we recommend
continued narcotic or non-narcotic analgesia, as
clinically indicated.

831 Photosensitivity reaction

832 A photosensitivity reaction occurs when normal tis-
833 sue is exposed to enough light to activate the photo-
834 sensitizing agent [7]. As each sensitizer has its own
835 characteristic activation energy and half-life, the
836 ability to have a photosensitivity reaction is sen-
837 sitizer dependent. In general, this reaction is sim-
838 ilar but more rapid to develop and more intense
839 than a sunburn. Even a few moments of sunlight
840 to a powerful photosensitizer such as Foscan[®] can
841 induce this reaction. Patients complain of pain in
842 the exposed area and swelling with burn can occur.
843 The severity of signs and symptoms will depend on
844 the intensity of light exposure and amount of sen-
845 sitizer remaining. Treatment to each burn is rec-
846 ommended with ice/cold compress, steroids, ele-
847 vation and pain control. If critical structures such
848 as airway, neck, orbits, etc. are exposed and begin
849 swelling, emergency treatment may be required,
850 perhaps as an inpatient. It should be emphasized
851 that patients are photosensitive starting from infu-
852 sion (not treatment). An ounce of sunlight preven-
853 tion beats a pound of cure.

854 To enhance elimination of the photosensitizer
855 from the skin one can employ the following pro-
856 cedure, if indicated. We suggest waiting at least 1
857 week post-treatment to try this. The fully covered
858 patient can carefully expose a 1 cm² area of skin
859 (forearm placed in a brown bag with a hole in it) at
860 sunset for a minute or two, but should pain occur,
861 this procedure should then be abandoned. If at 24 h
862 minimal sensitivity occurs, the patient can expose
863 more forearm skin for a bit longer and repeat this
864 several more times. By progressively increasing the
865 amount of skin exposed to limited amounts of twi-
866 light sunshine, the photosensitizer can be bleached
867 out fairly rapidly. Do not attempt this with Foscan[®]
868 and do not it at other times of the day.

869 Post-treatment

870 All patients' post-therapy should undergo several
871 days of steroids with taper. This minimizes local re-
872 action and swelling. Oral narcotic and non-narcotic
873 analgesia for 1–2 weeks is generally useful, though
874 some patients do not actually need these medica-
875 tions. We suggest a 1-week course of antibiotics
876 such as keflex or Augmenten. Patients are also en-
877 couraged to drink plenty of liquids. Every patient

878 must be reminded of sunlight precautions at this
879 point as well.

880 Patient selection

881 This is a key issue. One must ultimately ask how lo-
882 cal control of the chest wall will impact patients.
883 For patients with highly symptomatic chest wall le-
884 sions, even in the face of widespread disease, an
885 improved quality of life might be possible. How-
886 ever, should PDT create open wounds that will not
887 heal in the patient's lifetime, no obvious benefit is
888 to be gained. Given the natural history of recurrent
889 lesions to be poorly controlled and to grow, local
890 control and symptom prevention is an important
891 consideration. The timing of intervention is vari-
892 able; however, larger PDT fields take longer to heal
893 as does treatment of larger lesions. It is our pref-
894 erence to intervene with PDT prior to the patient's
895 back being against the wall. We have found that
896 many patients will not participate in any social ac-
897 tivity due to the physical and psychological prob-
898 lems associated with growing, visible tumors. Suc-
899 cessful PDT for these individuals is able to provide
900 extraordinary improvement in quality of life.

901 Wound healing

902 Fundamentally, PDT appears to swap ever-
903 progressing non-healing lesions with sterilized
904 wounds that can heal with excellent cosmetics
905 [34,61]. For lesions less than 1 cm in diameter and
906 isolated, healing time is measured in weeks. Larger
907 treatment fields can require months to heal.
908 Thicker and larger lesions often form eschars,
909 which we have found to be protective, painless and
910 infection free. It is our recommendation that PDT
911 fields be kept clean with as minimal intervention
912 as possible. Biopsy and wound surgery should be
913 avoided. In virtually all cases, lesions will close and
914 heal. Time to healing is delayed by chemotherapy.
915 In sterilized fields, the rare non-healing defect
916 caused by very large tumors necrosing can be
917 closed by flaps. This should only be attempted by
918 an experienced surgeon.

919 Retreatment

920 As recurrent lesions invade dermal lymphatics, they
921 have a propensity for wide cutaneous spread and
922 clinical re-occurrence. The PDT literature shows
923 patients are readily able to undergo multiple treat-
924 ment sessions and chest wall lesions are no excep-
925 tions. New lesions outside prior illumination fields
926 as well as the rarer rim progression can generally

be treated with the same drug/light parameters 927
as accomplished on the first session. Similar good 928
outcomes are expected. For the rarer, in field re- 929
currence more intense illumination should be con- 930
sidered. However, it is likely that the in-field re- 931
currence was due to under-dosage of light during 932
the initial PDT sessions. Several reports indicate 933
that re-treatment is well tolerated with excellent 934
response seen [34,61,72]. One should consider re- 935
treating patients on a case-by-case basis. Those 936
individuals with an isolated small recurrence may 937
benefit from a short course of radiation rather than 938
PDT induced photosensitivity. Also, as normal tissue 939
migration is required for wound healing, one might 940
not want to re-treat until the initial PDT treatment 941
fields have virtually healed. This will prevent the 942
development of excessive open wounds. 943

944 Conclusion

945 PDT can reliably salvage individuals with chest wall 946
recurrence despite fragile tissues from surgical, 947
radiation and chemotherapeutic intervention. PDT 948
can not only control chest wall recurrence, but of- 949
fer the potential for superior cosmetic results. This 950
is particularly noteworthy as these patients are all 951
too often denied any additional salvage, and are 952
left with daily growing reminders of their mortality.

953 Local treatment may have an impact on survival,
954 particularly if infected open tumor wounds can be
955 healed. In general survival is a function of control
956 of systemic spread. This is why most patients with
957 recurrent disease, even if thought to be contained
958 on the chest wall are initiated on systemic therapy.
959 No study of PDT for this patient population has been
960 large enough to analyze for improved survival. Even
961 if PDT may not significantly improve survival it can
962 improve the quality of life by eliminating obvious
963 signs and symptoms of disease. PDT also offers ex-
964 cellent pain control and by this criteria alone should
965 be considered beneficial.

966 Even with limited dosimetry, patients with chest
967 wall recurrence can be reliably salvaged by a vari-
968 ety of photosensitizing agents used in a variety
969 of treatment paradigms. Each agent and treatment
970 has its own risk to benefit ratio and cannot be inter-
971 changed. While excellent results can be obtained,
972 serious consequences can also arise. A large patient
973 literature exists reporting that low-dose Photofrin®
974 can offer high response rates with limited morbid-
975 ity even when inhomogeneous illumination occur.
976 Employing high dose Photofrin® and other sensitizers
977 does not appear to be as forgiving. While a num-
978 ber of trials have allowed for some conclusions on
979 how to optimize light and drug concentrations for

980 Photofrin[®], the same cannot be said for other sen-
 981 sitizers. Lower drug dose—higher light dose trials
 982 for other photosensitizers to enhance response and
 983 diminish side effects are needed.

984 Additional work needs to be done to enhance
 985 outcomes and minimize morbidity for patients with
 986 chest wall recurrence. Work on fluorescence will no
 987 doubt improve our ability to define what requires
 988 treatment rather than relying mainly on clinical ob-
 989 servation. Changes in fluorescence may allow bet-
 990 ter correlation with the success or failure of the
 991 treatment. It may also provide the basis for real
 992 time dosimetry. This would improve response and
 993 diminish side effects. As it stands micro lens fibers
 994 can be used successfully, but only a limited field
 995 can be illuminated at a time. This requires constant
 996 re-alignment and re-positioning for each treatment
 997 field. Not only is this time consuming and repet-
 998 itive, but lends itself to significant errors due to
 999 motion and potential geographical misses and over-
 1000 lap. As the micro-lens has limited illumination field
 1001 sizes, one may by necessity have to cut across tumor
 1002 or critical tissues which can have significant clin-
 1003 ical implications. A large homogeneous illumina-
 1004 tion field, perhaps created by individualized LED's
 1005 might offer simple and faster therapy and better
 1006 outcomes.

1007 Since PDT seems to work well as a last resort,
 1008 even in heavily treated tissue, one might wonder
 1009 if earlier intervention with PDT would improve the
 1010 outcome of the disease. Further, conceivably PDT
 1011 could be used as an adjunct to surgery to sterilize
 1012 the tumor bed. As most failures are local follow-
 1013 ing lumpectomy and radiation, PDT may improve
 1014 outcome. Finally, many patients who could main-
 1015 tain an intact breast, instead opt for mastectomy
 1016 due to a lack of radiation services. Possibly lumpec-
 1017 tomy bed PDT could offer these individuals breast
 1018 preservation as PDT treatment is far less expensive
 1019 and more mobile than the current 6 weeks of linear
 1020 accelerator based radiation. One can only hope that
 1021 this review will help stimulate interest in answering
 1022 these important questions.

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