Review Article

Photodynamic Therapy as a Treatment Option for Oral Cancer and Dysplasia

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Abstract

The challenge in cancer management is to find a balance between the intended therapeutic outcomes whilst preserving and maintaining function and aesthetics. This dilemma initiated ongoing efforts focusing on PDT which is now considered a historical re-utilized technique showing promising results but with many limitations. PDT has emerged as a successful and clinically acceptable therapeutic approach to the management of malignant and benign diseases. It is important to understand that PDT cannot completely replace other treatment modalities but can be used as a useful adjunct or as additional treatment.

Keywords: Dysplasia; Photodynamic therapy; Carcinoma; Treatment

Introduction

In order to successfully manage head and neck squamous cell carcinomas (HNSCC), it is imperative that function and aesthetics are maintained as much as possible. Improving loco-regional disease control rates has been somewhat the focus of research in the last 30-40 years. Non-surgical treatment approaches such as PDT can be applied to keep speech and swallowing function but with less than optimal improvements in survival. [1,2]

Nevertheless, it is immediately clear that advances in the management came at the expense of altering function and changing aesthetics. This was so that the ultimate goal of loco-regional control of the disease was achieved. [3,4]

The challenge in cancer management is to find a balance between the intended therapeutic outcomes whilst preserving and maintaining function and aesthetics. This dilemma initiated ongoing efforts focusing on PDT which is now considered a historical re-utilized technique showing promising results but with many limitations. Photodynamic therapy (PDT) is a treatment modality that is minimally invasive. Unlike ionizing radiation, PDT has the advantage that it can be applied repeatedly at the same site. PDT utilization in medicine had been widely accepted and it is an appealing option in oncology because the use of chemotherapy, ionizing radiation, or surgery does not preclude the use of PDT, and all of these approaches can be used in a patient who has received PDT.

PDT is not an alternative approach to the common used modalities however, there are certain circumstances were PDT can be used as an alternative approach. Although PDT is still emerging, it is already a successful and clinically approved therapeutic modality used for the management of neoplastic and nonmalignant diseases. [5]

PDT structure

PDT utilizes three components to achieve the intended effect on tumor cells and these essential components are: a photosensitizer (PS), light, and oxygen. The essential components are ineffective on tumor cells when exposed to the cells as single modalities. However, when they join together a highly reactive product, single, is formed causing significant toxicity resulting in cell death via apoptosis or necrosis. [6,7]

There are three mechanisms that cause the anti-tumor effects of PDT. These include the direct cytotoxic effects on tumor cells, damage to the tumor vascularity, and an inflammatory reaction leading to the development of systemic immunity. [8]

The therapeutic effect of PDT production of singlet oxygen

The basics of the photochemical reaction which initiates the process of tumor cell destruction is dependent on the excitation of the tissue oxygen located in the body by the injected

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photosensitizer. The oxygen molecules will be excited by the light activated photosensitizer which will change the oxygen molecule's electron energy level and initiate a new active species of oxygen in the area which is cytotoxic and that will produce part of our treatment goal. The destruction of the tumor cells in this process is considered a type II reaction. A type I reaction is active and cytotoxic, but it is less profound than type II. The production of hydrogen peroxide within the area that is being treated is a by-product which will undergo certain chemical pathways to result in the hydroxyl free radical that is highly cytotoxic. The effect of the type II reaction is more intense and it is believed that PDT is more dependent on this reaction than type I. [9]

Different types of PS will have different targets within the nearby cells (mitochondria, endoplasmic reticulum, lysosomes, etc), but generally all PS with different intensity will result in cell death and will initiate three cellular death pathways: apoptotic, necrotic and autophage-associated cell death. [10]

The PDT singlet oxygen pathway seems to be promising however; the tumor cells will activate several cytoprotective mechanisms to reduce the effect of PDT. The first mechanism identified is the over-expression of antioxidant molecules produced by the tumor cells to reduce the healing effect of PDT; that explains the full variation in cellular response to treatment. [11]

The second mechanism is the production of specific enzymes that is involved in the detoxification of the singlet oxygen production pathway. The tumor cells can target molecules in the production pathway of singlet oxygen. There is no enzyme that can break down singlet oxygen itself but targeting molecules in its production will influence the cytotoxicity of PDT. [12]

There is a third cytoprotective mechanism involving proteins. The proteins encoding genes are themselves induced by PDT. The encoding genes are part of signalling pathways. These pathways regulate PDT-induced apoptosis or contribute in the repair of lesions caused by oxidative stress. [13]

PDT effect on tumor vascularity

This subject still requires further research and work; nevertheless, the general principles of the effect have been established since 1963 following a study conducted by Castellini et al. that reported that PDT will lead to the disruption of the tumor circulation. There are various mechanisms that can describe the vascular influence of PDT. The primary mechanisms that best explain the PDT effect can be summarized in its effect on endothelial cells and platelet aggregation, and the wide scope of vascular changes which cumulatively induce hypoxia to the tumor cells. [14-17]

PDT initiates the immune system

By provoking a strong inflammatory response which can be observed as a strong edematous reaction. The initiation of what is called cell death-associated molecular patterns (CDAMP) is one of the major immune responses that is generated by PDT. These are proteins released in association with cellular death and they are mainly a result of damaged cellular organelles. Inflammatory cells are triggered and tumors undergoing PDT are rapidly invaded. The most important role of these cells is to eliminate the debris and dead cells induced by (CDAMP) and that will promote better healing. [18-20]

PDT for dysplasia and pre-malignancy

For PDT to be most effective, optimal light delivery or strength must be achieved. Certain factors including the size, shape, accessibility of the area being treated, and the depth of the lesion being treated must all be taken into consideration.

PDT can be delivered as an outpatient procedure or under general anesthesia. General anesthesia is typically used when wounds are affecting the throat and larynx.

Dysplastic lesions that are relatively small on the buccal mucosa, retromolar trigone, ventral and lateral oral tongue and the floor of mouth are treated effectively with PDT. [21]

The advantage of using PDT is that surrounding margins of visible lesions incorporating borders of normal mucosa can conservatively be included in the target location. Postoperative adjuvant therapy in patients with positive dysplasia margins can be used successfully. In photo-diagnosis, photosensitizers can be used to map subclinical regions of potential dysplastic cells. [22]

To identify the premalignant lesions (dysplasia) in the oral fibrotic mucosa when compared to hyperkeratotic and normal mucosa, ALA-induced PpIX fluorescence spectroscopy can be used. A study directed by Wang et al. after the topical application of 5-aminolevulinic acid (5-ALA, Levulan®) supports this.

Effective treatment depth is limited to several millimeters because the penetrating depth of the light is confined by its light absorption within tissue which is wavelength-dependent. For dysplastic mucosal lesions, a few millimeters depth of treatment is sufficient. Light absorption can be enhanced by reducing surface secretions which can lead to its expression. [23] ALA has been shown to be limited in its depth of action, sufficient for 1.5 mm thick lesions as shown in the results of Malley et al. It was also shown that ALA requires a number of treatments when used topically to reach a full clinical response. [24] Lesions greater than 3mm thickness with thick keratin layers and micro invasive carcinomas respond well to a single plane of interstitial light fibers placed through 18 gauge angiocatheters. Light fibers need to be placed beyond the dysplasia to accommodate for the light anisotropy that occurs at the end of each individual light fiber. [25] It is physically difficult to illuminate large lateral and ventral tongue dysplasia especially as illumination perpendicular to the mucous membrane may not be physically possible.

A prospective study was done by Rigual et al. for the the treatment of moderate to severe dysplasia and early T1 invasive oral and laryngeal carcinomas using pofirmer sodium, If tongue dysplasia extends to the adjacent floor of mouth, the concavity of the mucosal target creates technical illumination challenges. [26]

Jerjes et al. conducted a cohort study on 147 patients with potentially malignant oral disorders which were treated with PDT surface illumination. They suggested that PDT with 5-ALA and/or mTCHP photosensitizers offers an effective alternative treatment and demonstrated that patients with carcinoma in-situ, erythroplakia, and non-homogenous leukoplakia were the most sinister with the least response to PDT treatment and a high recurrence rate and risk of malignant transformation even after the PDT application when compared to the response of moderate dysplasia and homogenous leukoplakia. [27]

A range of photosensitizers including porfirmer sodium (Photofrin®)(25,26), aminolevulinic acid (Levulan®) [28] and mTHPC (Foscan®) [29] have been reported for the treatment of dysplasia. However,studies for the management of dysplasia alone have been very few, [26,29] For the palliative management of advanced head and neck invasive carcinomas, mTHPC is currently sanctioned by the European Union failing prior therapies. [28]

To facilitate PDT in the oropharynx, a group of researchers [21] have recently begun to investigate the role of transoral robotic surgical (TORS) technology. The oropharynx has not been a focus for head and neck PDT because of the limited access with traditional transoral approaches. Transrobotic surgery has been shown to not only be feasible but effective for oropharyngeal carcinoma. [24,30]

PDT uses in cancer managements

The sixth most common cancer in the world is oral and oropharyngeal carcinoma. The 5 years survival rate has not improved significantly during the past 30 years despite the evolution in management. [31]

Interventions and modalities being used to treat oral cancer is focused on controlling locoregional spread and recurrence of the tumor, and it can be prosperous in many cases. However, treatment options available such as surgery and radiation can be associated with astronomically immense morbidity and disfigurement for the patient; and the overall survival for the patient did not shift dramatically in the past 30 years.

PDT first clinical application as treatment modality for cancer was in the late 1970's for the treatment of bladder cancer in 5 patients. [32] Since then, PDT was under focus as new therapeutic alternative for the treatment of cancer with less morbidity to the patients. However, until now it did not reach the expected scientific approval due to some drawbacks.

In 1978, the first large series of patients were successfully treated with PDT by Dougherty et al. [5] They reported a 100% response rate when using HPD on a large variety of tumors.

In 2010, two systematic reviews [6,7] confirmed that PDT can be used as a treatment modality for malignant and premalignant non melanoma skin lesions.

In the head and neck region, Sharwani et al. conducted PDT in patients with suspicious oral leukoplakia. [8] Treatment of carcinoma using PDT in the head and neck is an attractive proposition. Maintaining facial and anatomical structure and function including facial disfigurement is imperative for good cosmetic and functional results.

Hopper et al. [9] investigated the role of mTHPC in patients with early oral squamous cell carcinoma. This was carried out in conducted an open label, multicenter study. Lou et al. [10] evaluated mTHPC in a phase I-II trial for the treatment of advanced head and neck cancer when all conventional methods had been exhausted. No loss of function by nerves encased by tumors was observed.

Benign conditions of the head and neck have also been treated by mTHPC induced PDT. Betz et al. [11] treated 11 patients with both lymphatic and venous malformations of the head and neck. Interstitial PDT was delivered. Significant improvement occurred in all patients with the best results occurring in patients with lymphatic malformations.

Surgery and radiotherapy give good cure rates in early stage head and neck cancer. The locoregional tumor control for T1 and T2 oral cavity and oropharyngeal carcinomas is between 72 and 93% with conventional therapies. [12,13] Unfortunately, due to the complex anatomy and physiology, both surgery and radiotherapy in the head and neck region can also result in significant morbidity. [14]

In early twenty-one century, the studies of Kubler, Copper and Hopper [15-17] show that PDT with second generation mTHPC gives tumor responses that are comparable with the outcomes of the conventional therapies, but with much less morbidity. A complete tumor response is not achieved after PDT and it is imperative that the option of retreatment with PDT or conventional therapy remains. [14] One of the advantages of PDT is that previous treatment with mTHPC-mediated PDT does not compromise salvage treatment with PDT, radiotherapy or surgery. [16,18,19] The protocol for treatment includes positioning the patient supine and intubated with either an endotracheal or nasotracheal laser-resistant tube when undergoing general anesthesia. A mouth gag, cheek retraction, and tongue retraction are essential for the exposure of the lesion. The laser must be secured but in a manner, that allows for flexible movements, fine adjustments, the ability to lock the laser in the appropriate position. Although the physician can hold the laser throughout the treatment, for accuracy pneumatic and robotic scope holders can be readily adapted to hold the laser with excellent results.

Discussion

Photodynamic therapy for tongue and sub-glottic carcinoma

Total glossectomy and laryngectomy, when indicated, were once more commonplace for tumors at the tongue base along with dissection of the cervical lymphatic chain. [29] It is known that there is an increase in local failure rate when positive margins are present. Planned postoperative radiotherapy is indicated for advanced and/or recurrent disease. The addition of

chemotherapy to the management of advanced base of tongue carcinoma is ongoing, and the results from this treatment option are not widely reported in the literature. [30]

Recent advances in the application of minimally invasive technologies to tongue base cancers have resulted in similar loco-regional control rates but with decreased morbidity compared to larger open procedures. These advanced surgical techniques require additional training and equipment to be performed but reported results are promising. [31] PDT is currently being used in the management of several cancers including: head and neck, brain, lung, pancreas, intra-peritoneal cavity, breast, prostate and skin. It has also proven to be very successful in treating vascular anomalies. PDT will have a leading role in minimally-invasive surgical oncology after a more and more evidence of successful treatments, especially with the development of image-guided iPDT. [31-33]

Ultrasound imaging guides the optical fibers to the appropriate disease volume. Given its accuracy, it allows for the guidance of delivery apparatus away from vital structures and ensures that delivery needles are placed parallel for improved dosage administration profiles. [31,32,34] Treatment for subglottic carcinoma commonly involves wide surgical resection and external beam radiation. A combination of surgery and photodynamic therapy to the margin in this case enabled a complete response whilst reducing surgical morbidity for the patient. [35-37] T has been reported by Nhembe et al. that there was curative treatment of a subglottic carcinoma with a combination of surgical "debulking and" or "intraluminal'' photodynamic therapy. There has been no evidence of recurrence in the 18-month follow-up period and their histo-pathological studies showed no evidence of dysplasia or dysplasia with clinical symptoms.

Photodynamic therapy for a treatment of head and neck malformations

The gold standard treatment of lymphatic malformations is surgery [38-40] and the recurrence rates after incomplete resection vary between 35% and 100% (41). Sclerotherapy has been investigated as a treatment option in recent years when surgery is difficult in inaccessible or challenging areas. [24-44] The advantage of PDT over sclerotherapy is that a wider variety of lesions cab be treated with lower side effects.

Interstitial PDT with mTHPC as a photosensitizer seems to be a safe, effective, symptom-targeted treatment option for complex benign vascular lesions. Depending on the extent and site of the lesion, fibre placement may be performed clinically or under image guidance. [45] The method compares favorably with conventional treatment modalities for head and neck lesions, because it can be repeated a number of times with very low neurovascular side effects.

For venous malformations, PDT may offer a viable alternative as a monotherapy as large and complex venous malformations seem to be treatable with good outcomes concerning symptom-relief and only minor chances for adverse events (especially concerning neurovascular structures). [46,47] For PDT used in the treatment of cystic hygroma, Zaid et al. [48] report the outcome of one round of photodynamic therapy in the management of an extensive macrocystic hygroma in an infant. There was considerable improvement in neck deformity and relative restoration of the midline symmetry.

Photodynamic therapy for solitary giant neurofibroma

Hamdoon et al. [49] presented a patient with a lesion causing refractory pain and dysphagia. As a result of PDT, there was a significant reduction in the size of the lesion after just one round of treatment. Symptoms have shown resolution with no morbidity. Surgery is still the gold-standard treatment for neurofibromas but again with a challenge in head and neck because of the significantly complicated anatomy. [50,51]

Radiotherapy cannot be carried out successfully when diseases present as a diffuse form. The lesions may shrink by radiotherapy and therefore have their growth controlled. Intensity-modulated radiotherapy was shown to be effective in controlling extensive or recurrent juvenile angiofibroma. [52] PDT will be an excellent modality for treatment of head and neck neurofibromas, but further trials need to be attempted.

Transoral robotic photodynamic therapy for the oro-pharynx

Even under general anesthesia with traditional laryngoscopes, exposing the oropharyngeal mucosa is limited by its anatomy. To overcome this, TORS can facilitate excellent three-dimensional visualization with safe, accurate and stable delivery of PDT to the oropharynx. An advantage of this is that the application of PDT can be extended to a site previously limited by achieving adequate exposure. [53]

Photochemical internalization

Berg et al. in 1999 [54] examined photochemical internalization (PCI) as a novel technique for releasing macromolecules from endosomes and lysosomes into the cytosol. They concluded that PCI would be an ideal drug delivery tool in gene therapy and that it may potentially be combined with other principles like the use of disease-specific drugs, opening a possibility of obtaining substantial synergistic effects in the specificity of drugs for target cells such as in cancer treatments. In 2001, [55] the same group conducted an *in vivo* study to evaluate the therapeutic potential of PCI of the type I ribosomal-inactivating protein gelonin, where the results showed that the synergistic effect of combining photoactivation of photosensitizer located in endocytic vesicles and gelonin is indeed a result of PCI of gelonin. In 2005, [56] they then introduced bleomycin as the chemotherapeutic agent of choice for PCI.

It is reported that two clinical and pathological parameters are most important when it comes to assessing the progression, recurrence or morbidity of a tumor; the surgical margin and nodal involvement. [57] The surgical margin is a major player in assessing the disease status. Norum et al. in 2009 [58] showed that PCI was more effective that PDT in the tumor periphery *in vitro*.

Conclusion

In summary, PDT is a promising new method and has been

shown to have significant parameters of success in the treatment of head and neck lesions. As a relatively new treatment modality further studies are needed to show its potential and its range of applications as a single treatment or in combination with other approved or experimental therapeutic approaches.

The main and most important advantage of PDT compared with surgery or radiotherapy is that reduced long-term morbidity. PDT does not compromise future treatment options for recurrent, residual or second primary disease. Research efforts are focusing on optimizing treatment options by way of improving photosensitizer drug development, light delivery techniques, and devices and the development of real time monitoring during the treatments.

Conflict of Interest

All authors disclose that there was no conflict of interest.

References

1. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, et al. Photodynamic therapy. J Natl Cancer Inst. 1998; 90: 889-905.
2. Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. Nat Rev Cancer. 2003; 3: 380-387.
3. Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, et al. Photodynamic therapy of cancer: An update .CA Cancer J Clin. 2011; 61: 252-253.
4. Kelly JF, Snell ME. Hematoporphyrin derivative: A possible aid in the diagnosis and therapy of carcinoma of the bladder. J Urol. 1976; 115:150-151.
5. Dougherty TJ, Kaufman JE, Goldfarb A, Weishaupt KR, Boyle D, Mittleman A. Photoradiation therapy for the treatment of malignant tumors. Cancer Res. 1978; 38: 2628-2635.
6. Fayter D, Corbett M, Heirs M, Fox D, Eastwood A. A systematic review of photodynamic therapy in the treatment of precancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess. 2010; 14: 1-288.
7. Gao F, Bai Y, Ma SR, Liu F, Li ZS. Systematic review: photodynamic therapy for unresectable cholangiocarcinoma. J Hepatobiliary Pancreat Sci. 2010; 17: 125-131.
8. Sharwani A, Jerjes W, Salih V, MacRobert AJ, El-Maaytah M, Khalil HS, et al. Fluorescence spectroscopy combined with 5- aminolevulinic acid-induced protoporphyrin IX fluorescence in detecting oral pre-malignancy. J Photochem Photobiol B 2006; 83: 27-33.
9. Hopper C, Kubler A, Lewis H, Tan IB, Putnam G. mTHPC-mediated photodynamic therapy for early oral squamous cell carcinoma. International journal of cancer 2004; 111: 138-146.
10. Lou PJ, Jager HR, Jones L, Theodossy T, Bown SG, Hopper C. Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. Br J Cancer 2004; 91: 441-446.
11. Betz CS, Jager HR, Brookes JA, Richards R, Leunig A, Hopper C. Interstitial photodynamic therapy for a symptom-targeted treatment of complex vascular malformations in the head and neck region. Lasers Surg Med 2007; 39: 571-582.
12. Fein DA, Mendenhall WM, Parsons JT, McCarty PJ, Stringer SP, Million RR, et al. Carcinoma of the oral tongue: a comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck 1994; 16: 358-365.
13. Gomez D, Faucher A, Picot V, Siberchicot F, Renaud-Salis JL, Bussières E, et al. Outcome of squamous cell carcinoma of the gingiva: a follow-up study of 83 cases. J Craniomaxillofac Surg 2000; 28: 331-335.
14. Nyst HJ, Tan IB, Stewart FA, Balm AJ. Is photodynamic therapy a good alternative to surgery and radiotherapy in the treatment of head and neck cancer? Photodiagnosis and Photodynamic Therapy 2009; 6: 3-11.
15. Copper MP, Tan IB, Oppelaar H, Ruevekamp MC, Stewart FA. Meta-tetra (hydroxyphenyl)chlorin photodynamic therapy in early-stage squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 2003; 129: 709-711.
16. Hopper C, Kubler A, Lewis H, Tan IB, Putnam G. mTHPC mediated photodynamic therapy for early oral squamous cell carcinoma. Int J Cancer 2004; 111: 138-146.
17. Kubler AC, De CJ, Hopper C, Leonard AG, Putnam G. Treatment of squamous cell carcinoma of the lip using Foscanmediated photodynamic therapy. Int J Oral Maxillofac Surg 2001; 30: 504-509.
18. Hopper C. Photodynamic therapy: A clinical reality in the treatment of cancer. Lancet Oncol 2000; 1: 212-219.
19. Hornung R, Walt H, Crompton NE, Keefe KA, Jentsch B, Perewusnyk G, et al. m-THPC-mediated photodynamic therapy (PDT) does not induce resistance to chemotherapy, radiotherapy or PDT on human breast cancer cells in vitro. Photochem Photobiol 1998; 68: 569-574.
20. Quon H, Grossman CE, Finlay JC, Zhu TC, Clemmens CS, Malloy KM, et al. Photodynamic therapy in the management of pre-malignant head and neck mucosal dysplasia and microinvasive carcinoma Photodiagnosis and Photodynamic Therapy 2011; 8: 75-85.
21. Wang CY, Tsai T, Chiang CP, Chen HM, Chen CT. Improved diagnosis of oral premalignant lesions in submucous fibrosis patients with 5-aminolevulinic acid induced PpIX fluorescence. J Biomed Opt 2009; 14: 044026.
22. Taroni P, Pifferi A, Torricelli A, Comelli D, Cubeddu R. In vivo absorption and scattering spectroscopy of biological tissues. Photochem Photobiol Sci 2003; 2: 124-129.
23. O'Malley Jr BW, Weinstein GS, Snyder W, Hockstein NG. Transoral robotic surgery (TORS) for base of tongue neoplasms. Laryngoscope 2006; 116: 1465-1472.
24. Biel MA. Photodynamic therapy treatment of early oral and laryngeal cancers. Photochem Photobiol 2007; 83: 1063-1068.
25. Rigual NR, Thankappan K, Cooper M, Sullivan MA, Dougherty T, Popat SR, et al. Photodynamic therapy for head and neck dysplasia and cancer. Arch Otolaryngol Head Neck Surg 2009; 135: 784-788.
26. Yu CH, Lin HP, Chen HM, Yang H, Wang YP, Chiang CP. Comparison of clinical outcomes of oral erythroleukoplakia treated with photodynamic therapy using either light emitting diode or laser light. Lasers Surg Med 2009; 41: 628-633.
27. Copper MP, Triesscheijn M, Tan IB, Ruevekamp MC, Stewart FA. Photodynamic therapy in the treatment of multiple primary tumours in the head and neck, located to the oral cavity and oropharynx. Clin Otolaryngol 2007; 32: 185-189.
28. Weinstein GS, O'Malley Jr BW, Snyder W, Sherman E, Quon H. Transoral robotic surgery: radical tonsillectomy. Arch Otolaryngol Head Neck Surg 2007; 133: 1220-1226.
29. O'Neill JP, Hughes JP, Manning KP, Fenton JE. Controversies in the management of tongue base cancer. Ir J Med Sci 2009; 178: 1–5.
30. Jones AS, Rafferty M, Fenton JE, Jones TM, Husband DJ. Treatment of squamous cell carcinoma of the tongue base: irradiation, surgery, or palliation? Ann Otol Rhinol Laryngol 2007; 116: 92-99.
31. Jager HR, Taylor MN, Theodossy T, Hopper C. MR imaging guided interstitial photodynamic laser therapy for advanced head and neck tumors. AJNR Am J Neuroradiol 2005; 26: 1193-1200.
32. Vaidya A, Sun Y, Ke T, Jeong EK, Lu ZR. Contrast enhanced MRI-guided photodynamic therapy for site-specific cancer treatment. Magn Reson Med 2006; 56: 761-767.
33. Jerjes W, Upile T, Hamdoon Z, Nhembe F, Bhandari R, Mackay S, et al. Ultrasound-guided photodynamic therapy for deep seated pathologies: Prospective study. Lasers Surg Med 2009; 41: 612-621.

34. Hopper C, Kubler A, Lewis H, Tan IB, Putnam G. mTHPC mediated photodynamic therapy for early oral squamous cell carcinoma. Int J Cancer 2004; 111: 138-146.

35. Jerjes W, Upile T, Abbas S, Vincent A, Hopper C. The developing role of photodynamic therapy in multidisciplinary oncological care. Oncol News 2008; 3: 12-15.

36. Jerjes W, Upile T, Betz CS, El-Maaytah M, Abbas S, Wright A, et al. The application of photodynamic therapy in the head and neck. Dent Update 2007; 34: 478-480.

37. Lou PJ, Jǒger HR, Jones L, Theodossy T, Bown SG, Hopper C. Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. Br J Cancer 2004; 91: 441-446.

38. Nhembe F, Jerjes W, Upile T, Hamdoon Z, Vaz F, Hopper C. Subglottic carcinoma treated with surgery and adjuvant photodynamic therapy Photodiagnosis and Photodynamic Therapy 2010; 7: 284-287.

39. Bloom DC, Perkins JA, Manning SC. Management of lymphatic malformations. Curr Opin Otolaryngol Head Neck Surg 2004; 12: 500-504.

40. Kennedy TL, Whitaker M, Pellitteri P, Wood WE. Cystic hygroma/lymphangioma: A rational approach to management. Laryngoscope 2001; 111: 1929-1937.

41. Smith RJ. Lymphatic malformations. Lymphatics Res Biol 2004; 2: 25-31.

42. Lee BB, Kim YW, Seo JM, Hwang JH, Do YS, Kim DI, et al. Current concepts in lymphatic malformation. Vasc Endovasc Surg 2005; 39: 67-81.

43. Mathur NN, Rana I, Bothra R, Dhawan R, Kathuria G, Pradhan T. Bleomycin sclerotherapy in congenital lymphatic and vascular malformations of head and neck. Int J Pediatr Otorhinolaryngol 2005; 69: 75-80.

44. Okazaki T, Iwatani S, Yanai T, Kobayashi H, Kato Y, Marusasa T, et al. Treatment of lymphangioma in children: Our experience of 128 cases. J Pediatr Surg 2007; 42: 386-389.

45. Betz C, Rolf H, Brookes J , Richards R, Leunig A, Hopper C. Interstitial Photodynamic Therapy for a Symptom-Targeted Treatment of Complex Vascular Malformations in the Head and Neck Region Lasers in Surgery and Medicine 2007; 581.

46. Sarig O, Kimel S, Orenstein A. Laser treatment of venous malformations. Ann Plast Surg 2006; 57: 20-24.

47. Scherer K, Waner M. Nd: YAG lasers (1,064 nm) in the treatment of venous malformations of the face and neck: Challenges and benefits. Lasers Med Sci 2007.

48. Hamdoon Z, Jerjes W, Upile T, Akram S, Hopper C. Cystic hygroma treated with ultrasound guided interstitial photodynamic therapy: Case study Photodiagnosis and Photodynamic Therapy 2010; 7: 179-182.

49. Hamdoon Z, Jerjes W, Al-Delayme R, Hoppe C. Solitary giant neurofibroma of the neck subjected to photodynamic therapy: case study. Head & Neck Oncology 2012, 4: 30.

50. Marocchio LS, Oliveira DT, Pereira MC, Soares CT, Fleury RN: Sporadic and multiple neurofibromas in the head and neck region: a retrospective study of 33 years. Clin Oral Investig 2007; 11: 165-169.

51. Shin M, Ueki K, Kurita H, Kirino T. Malignant transformation of a vestibular schwannoma after gamma knife radiosurgery. Lancet 2002, 360: 309-310.

52. Kuppersmith RB, Teh BS, Donovan DT, Mai WY, Chiu JK, Woo SY, et al. The use of intensity modulated radiotherapy for the treatment of extensive and recurrent juvenile angiofibroma. Int J Pediatr Otorhinolaryngol 2000; 52: 261-268.

53. Quon H, Finlay J, Cengel K, Zhu T, O'Malley B, Weinstein G. Transoral robotic photodynamic therapy for the oropharynx Photodiagnosis and Photodynamic Therapy 2011; 8: 64-67.

54. Berg K, Selbo PK, Prasmickaite L, Tjelle TE, Sandvig K, Moan J, et al. Photochemical internalization: a novel technology for delivery of macromolecules into cytosol. Cancer Res. 1999; 59: 1180-1183.

55. Selbo PK, Sivam G, Fodstad O, Sandvig K, Berg K. In vivo documentation of photochemical internalization, a novel approach to site specific cancer therapy. Int J Cancer. 2001; 92: 761-766.

56. Berg K, Dietze A, Kaalhus O, Høgset A. Site-specific drug delivery by photochemical internalization enhances the antitumor effect of bleomycin. Clin Cancer Res. 2005; 11: 8476-8485.

57. Jerjes W, Upile T, Petrie A, Riskalla A, Hamdoon Z, Vourvachis M, et al. Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients. Head Neck Oncol 2010; 2:9.

58. Norum OJ, Gaustad JV, Angell-Petersen E, Rofstad EK, Peng Q, Giercksky KE, et al. Photochemical internalization of bleomycin is superior to photodynamic therapy due to the therapeutic effect in the tumor periphery. Photochem Photobiol. 2009; 85: 740-749.