

Article original

Photodynamic therapy as salvage treatment for recurrent head and neck cancer

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Abstract – Head and neck cancers often lead to disfiguration or functional impairments after treatment. Local recurrence occurs in around 60% of cases and most of them can not be retreated. Photodynamic therapy (PDT) can be an alternative treatment.

In a serie of 10 patients with recurrent squamous cell carcinoma of the head and neck that have failed prior therapies and are unsuitable for conventional curative therapy, PDT treatment has been used.

Eight patients have shown complete cicatrisation. Seven patients were cured after the follow up period up to 53 months. Three patients died (one outside etiology). Quality of life was considered as very much for 6 out of 10 patients, quite a bit for 1 patient, a little for 2 patients and not at all for 1 patient. Clinical benefit was evaluated as very much for 6 patients out of 10, quite a bit for 2 patients, a little for 1 patient and not at all for 1 patient.

PDT can be proposed to patients with head and neck cancer in palliative situation. It could be a therapeutic solution for selected cases with good outcomes. PDT offers patients a unique chance of remission and increased life expectancy compared with palliative treatments.

Mots clés :
cancer de la tête
et du cou / traitement
de sauvetage / thérapie
photodynamique /
photosensibilisants

Résumé – La thérapie photodynamique comme traitement de sauvetage pour les récides des cancers des voies aéro-digestives supérieures. Les cancers de la tête et du cou conduisent souvent à des séquelles esthétiques ou fonctionnelles majeures après traitement. Des récides locales sont observées dans environ 60 % des cas et la majorité ne peut pas être retraitée à nouveau. La thérapie photodynamique (PDT) peut être une possibilité de prise en charge alternative.

Dans une série de 10 patients présentant une récide d'un carcinome épidermoïde des voies aéro-digestives supérieures qui n'est plus accessible à traitement curatif conventionnel, la PDT a été utilisée.

Huit patients ont montré une cicatrisation complète. Sept patients étaient considérés comme guéris après une période de surveillance allant jusqu'à 53 mois. Trois patients sont décédés (dont un d'une cause extérieure au contexte carcinologique). La qualité de vie a été considérée comme très bonne pour 6 patients sur 10, bonne pour 1 patient, moyenne pour 2 patients et mauvaise pour 1 patient.

La PDT est une option thérapeutique qui peut être proposée aux patients atteints de cancers des voies aéro-digestives supérieures et placés en situation de prise en charge palliative. Cela pourrait être une possibilité de prise en charge pour des patients bien sélectionnés qui permettrait d'obtenir de bons résultats. La PDT a offert à ces patients une chance unique de rémission de la maladie et a amélioré indéniablement le taux de survie par rapport à la prise en charge palliative qui était la seule alternative.

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Head and neck cancer represents a large problem worldwide. The incidence varying from 5% in developed countries to as high as 30% in developing countries [1]. Over 90% of these cancers consist of squamous cell carcinoma [2]. Squamous cell carcinoma is an extremely aggressive disease. Estimated tumour doubling times range from 9.5 to 320 days, with local recurrences growing faster [1]. Standard treatment for these tumours is surgery and/or radiotherapy and/or chemotherapy. The particular localisation of head and neck cancers often leads to disfiguration or functional impairments. Survival rates decreases with the stage of the tumour: more than 80% for stage I and II, less than 50% for stage III or IV [3]. Local recurrence after curative intent radiation alone or in combination with surgery and/or chemotherapy may occur in around 60% of cases [4]. Most of the recurrences cannot be retreated by surgery, radiotherapy and/or chemotherapy and, therefore, treatment is essentially palliative. Overall, fewer than 15% of patients who fail first-line treatment can be successfully retreated [5].

Photodynamic therapy (PDT) is a very efficient alternative treatment for recurrent cancer of the oral cavity with excellent long term functional and cosmetic outcomes [3, 6, 7]. The basis of PDT is the combination of a photosensitizer (Foscan[®] in our study) and light which causes a cytotoxic effect to cancerous tissue. The biological effects of PDT are primarily mediated either by the generation of reactive oxygen species, such as singlet oxygen (¹O₂) or by the production of oxygen free radicals which cause tumour cell death by intracellular oxygenation and vascular shutdown mechanisms [8]. Foscan[®] (meta-tetra(hydroxyphenyl) chlorine: mTHPC) (Fig. 1) is a second generation photosensitizer with favorable photochemical and immunological properties [9]. The ability of PDT to generate apoptotic cells is acknowledged to be an important factor in the PDT treatment efficacy. The photosensitizer is usually administrated intravenously several hours prior to illumination [10]. During the time interval between systemic photosensitizer injection and illumination, a concentration ratio between the tumour and surrounding normal tissue occurs [11]. At the time when this ratio is optimum, illumination by a non thermal light of the appropriate wavelength activates the photosensitizer. It has been demonstrated by Peng et al. [12] that tumour cells have higher accumulation of photosensitizer than the surrounding normal tissue. As a result, when the photosensitizer is activated, tumour cells are selectively destroyed. This selective destruction is a major advantage. Local normal tissue is preserved without sacrificing the efficacy of tumour control [13]. In addition, PDT does not have the cumulative toxicity associated with ionising radiation and can be applied safely to previous irradiated tissues [14]. Therefore, PDT has considerable potential for patients with locally persistent or recurrent disease after surgery or radiotherapy.

The primary objective of our photodynamic therapy treatment is to assess overall tumour response in patients with

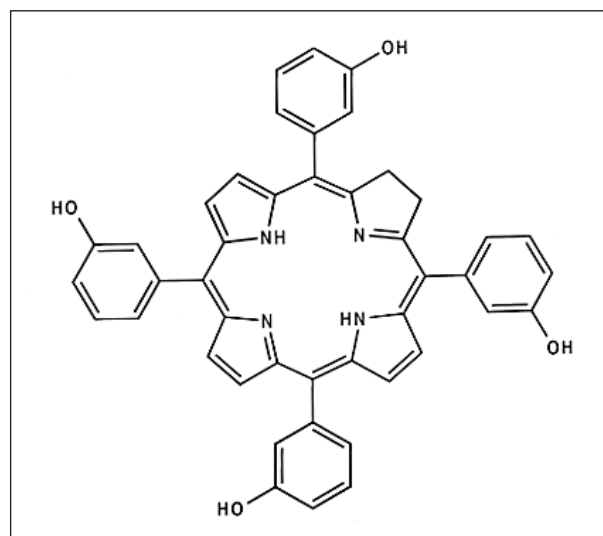


Fig. 1. Chemical structure of Foscan[®].
Fig. 1. Structure chimique du Foscan[®].

advanced squamous cell carcinoma of the head and neck who have failed prior therapies and are unsuitable for curative therapy with radiotherapy, surgery or systemic chemotherapy.

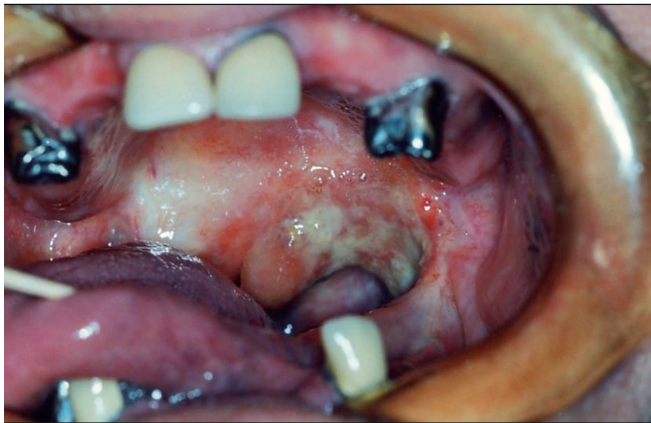
Here we report a series of 10 patients who underwent photodynamic therapy for recurrent or advanced head and neck cancer, not suitable for other standard treatment options, instead of palliative surgery or palliative chemotherapy. Tumour response and individual clinical quality of life benefit were investigated.

Patients and methods

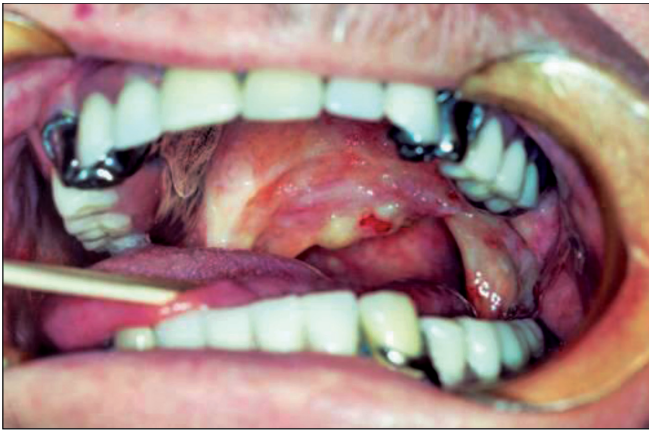
Patients

From 2003 to 2005, 10 consecutive patients, 8 men and 2 women, underwent photodynamic therapy for recurrent or advanced head and neck cancer. After a protocolised check up and staging, a multidisciplinary decision meeting, including therapeutic and peritherapeutic teams, allows the physician to propose a therapeutic scheme which was palliative for all patients due to the importance of the volume or the localisation of the tumour. Photodynamic therapy has been proposed and accepted by these patients.

All patients were more than 18-year-old man or non pregnant woman with an advanced histological confirmed squamous cell carcinoma of head and neck, documented to have failed prior therapies and unsuitable for curative therapy with radiotherapy, surgery or systemic chemotherapy. A limited metastatic disease is accepted if no premature withdrawal is expected. Each patient must be willing and able to provide written informed consent. The tumour was always single,



a



b

Fig. 2. Left soft palate recurrent squamous cell carcinoma before treatment (a) and 8 weeks after PDT (b) (patient # 5).

Fig. 2. Récidive d'un carcinome épidermoïde du voile du palais avant le traitement (a) et 8 semaines après la PDT (b) (patient # 5).

locally accessible and visible for unrestricted illumination with microlens fiber, with a depth less than 10 mm assessed by RMI (Fig. 2). Tissue cannot be illuminated more than 10 mm depth.

Methods

Photosensitizer (Foscan[®]) was administrated by injection at a dose of 0.15 mg/kg body weight, four days (90 to 110 h) prior to illumination. Illumination was insured by a laser with a wavelength of 652 (± 3) nm, by no more than 3 overlapping spots. Each should not exceed 4 cm. Only tumour and border have to be illuminated, all tissues around are hidden by shields. Shielding is important because 50% of incident light is back-scattered, so tissues within mouth but not within original spot may be illuminated. Therefore, this unwanted illumination can result in unwanted tissue damage. Total dose light is 20 J/cm². Illumination is made during 200 s, the light dose rate is

0.1 W/cm², it includes at least 0.5 cm border all round the tumour in order to destroy non visible tumour cells. All the procedure must be insured under reduced light conditions in operating room.

Photodynamic therapy is potentially painful, general anaesthesia is therefore advised. Each patient has a pre-procedural treatment including preemptive analgesia and steroids to reduce swelling. Postoperative analgesia must use opioid based analgesia.

The baseline is recorded 4 days before illumination which corresponds to the injection of the photosensitizer. All postoperative evaluations are made at week 8, 12, 16, 28 and 40. Tumour response is evaluated as complete or partial. All patients are asked to quantify any treatment benefit experienced on a 4 point scale: 1 not at all, 2 a little, 3 quite a bit, 4 very much. Quality of life is also evaluated at the same time.

Results

Patients characteristics are detailed in Table I. The disease was staged according to the VIth edition of the TNM classification established by the UICC/AJCC [15]. First tumours of each patient were noted as T1 (3 patients), T2 (5 cases) and T3 (2 patients). Five patients were treated by association surgery/radiotherapy, 3 by radiotherapy exclusively, one by association radiotherapy/chemotherapy and one by chemotherapy exclusively. Recurrences were noted after from 6 months to 14 years (mean: 4 years and 4 months). PDT treatment has been used and the results of PDT were as follow: 8 patients (80%) have shown complete tumour response after from 12 to 20 weeks after PDT (mean: 15 weeks). Seven (70%) patients were considered as cured after the follow up period from 28 to 53 months (mean: 40.5 months). Three patients (30%) died after from 4 to 12 months after PDT, 2 due to tumour evolution and 1 from pneumopathy (outside etiology). The patient who died after pneumopathy has shown complete tumour response. Only one patient had 2 PDT treatments after a second recurrence of the same tumour and was considered as cured after all. One patient experienced a severe complication after PDT, a major extensive swelling of head and neck tissues has imposed the necessity of a transitory tracheotomy.

Evaluation of quality of life was considered as very much for 6 out of 10 patients (60%), quite a bit for 1 patient (10%), a little for 2 patients (20%) and not at all for 1 patient (10%). Clinical benefit was evaluated as very much for 6 patients out of 10 (60%), quite a bit for 2 patients (20%), a little for 1 patient (10%) and not at all for 1 patient (10%).

Discussion

PDT has demonstrated its efficiency for patients with recurrent or advanced squamous cell carcinoma of the head and neck

Table I. Patients characteristics.
Tableau I. Caractéristiques des patients.

Patient	Sex / Age	First cancer localisation / date / staging	First cancer treatment	Recurrence localisation / date / staging	PDT treatment	Complication	Outcome / quality of life / clinical benefit
1	M / 74	Oropharynx / 1983 / T2	Radiotherapy / Chemotherapy	Soft palate / 2003 / T2	March 2003		Complete cicatrisation at 16 weeks Cured at 51 months Quality of life: very much Clinical benefit: very much
2	M / 70	Mouth floor / 1991 / T1	Surgery / Radiotherapy	Mouth floor / 2005 / Tis	May 2005		Complete cicatrisation at 20 weeks Cured at 28 months Quality of life: very much Clinical benefit: very much
3	M / 48	Oropharynx 4 localisations / 1999 / T3	Surgery / Radiotherapy	Mandibular gum / 2003 / T2	April 2003		Complete cicatrisation at 12 weeks Cured at 53 months Quality of life: very much Clinical benefit: very much
4	F / 66	Laryngopharynx / 2001 / T1	Surgery / Radiotherapy	Soft palate / 2004 / Tis	September 2004	Major extensive swelling	Complete cicatrisation at 20 weeks Cured at 36 months Quality of life: a little Clinical benefit: quite a bit
5	M / 71	Soft palate / 2002 / T3	Radiotherapy	Soft palate / 2004 / T3	March 2004		Complete cicatrisation at 12 weeks Dead at 12 months by pneumopathy Quality of life: quite a bit Clinical benefit: quite a bit

Table I. Continued.
Tableau I. Suite.

Patient	Sex / Age	First cancer localisation / date / staging	First cancer treatment	Recurrence localisation / date / staging	PDT treatment	Complication	Outcome / quality of life / clinical benefit
6	M / 77	Mouth floor / 2003 / T2	Radiotherapy	Mouth floor / 2003 / T3	December 2003		Dead at 6 months, tumour evolution Quality of life: a little Clinical benefit: a little
7	F / 45	Tongue / 2000 / T2	Surgery / Radiotherapy	Tongue / 2003 / T3	December 2003		Dead at 4 months, tumour evolution Quality of life: not at all Clinical benefit: not at all
8	M / 52	Pharyngolarynx / 2001 / T2	Chemotherapy	Pharyngolarynx / 2004 / Tis	May 2004		Second recurrence at 16 months cured with second PDT in september 2005 Complete cicatrisation at 15 weeks Cured at 24 months Quality of life: very much Clinical benefit: very much
9	M / 66	Retromolar trigon and mouth floor / 2002 / T1	Radiotherapy	Mouth floor / 2003 / T1	June 2003		Complete cicatrisation at 12 weeks Cured at 51 months Quality of life: very much Clinical benefit: very much
10	M / 70	Mouth floor / 2001 / T2	Surgery / Radiotherapy	Mouth floor / 2004 / T1	May 2004		Complete cicatrisation at 14 weeks Cured at 40 months Quality of life: very much Clinical benefit: very much

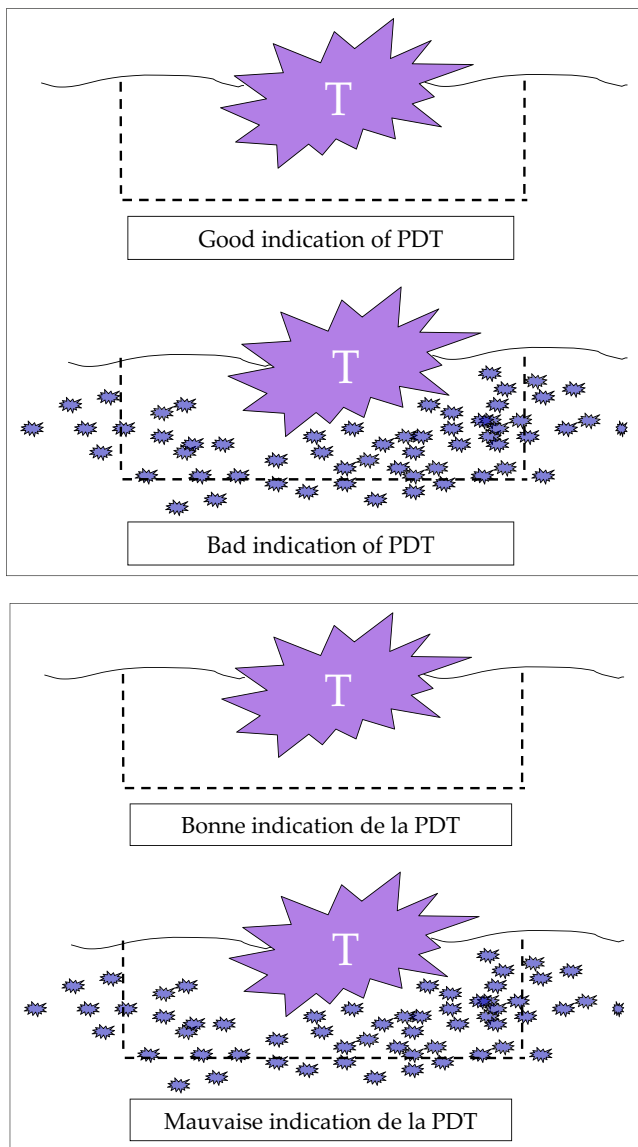




Fig. 3. Good or bad PDT indications.
 T: tumour, ---: limits of illumination, : cancerous cells.
 Fig. 3. Bonne et mauvaise indications de la PDT.
 T : tumeur, --- : limites de l'illumination,  : cellules cancéreuses.

who have failed prior therapies and are unsuitable for curative therapy with radiotherapy, surgery or systemic chemotherapy.

Head and neck recurrent cancer treatment and reconstruction remain a challenge. Curative surgery or radiotherapy of these tumours can be very mutilating or even impossible [16]. Multiple aesthetic or functional sequelae are induced. Even if the use of free flaps (free radial forearm flap in particular) or local flaps (pectoralis major flap, temporalis flap, infra hyoid musculo cutaneous flap) can reduce these sequelae [17, 18], quality of life remains often perturbed and success rate is low.

Radiotherapy is associated with a number of distressing or disabling side effects including xerostomia, mucositis, loss of taste and smell, laryngeal dysfunction, skin erythema and it may also cause skin breakdown or osteonecrosis [1]. For recurrent cancer of head and neck, radiotherapy has often been used for the first treatment and therefore, can not be used again. Cumulative dose would be too high.

PDT has the advantage of being a local treatment that spares tissue architecture while destroying malignant cells. After treatment, reepithelialization occurs with little or no scarring [1].

In our study, quality of life has been considered as very much or quite a bit for 7 patients out of 10 (70%), tumour response was complete for 8 out of 10 patients (80%) and clinical benefit has been noted as very much or quite a bit for 8 patients out of 10 (80%).

Successful PDT treatment is dependant on using effective photosensitizers, in an appropriate dosage, and accurately controlling the required amount of light to the tumour area [3]. All cancerous cells have to be illuminated in order to be destroyed, tumour must be therefore limited with no cancerous cells disseminated in local normal tissue (Fig. 3). The ability to homogeneously illuminate lesions via a microlens is limited [19, 20]. The periphery of tumours might receive insufficient light dose to completely eradicate the cancer cells, nevertheless Yang et al. [13] have demonstrated that PDT could suppress the migration and invasion of head and neck cancer cells lines (KJ-1 and Ca9-22) in vitro, which is encouraging for in vivo studies.

Patient selection is important and technical deficiencies for successful head and neck PDT should not be minimized [19]. While illumination is short, the recovery appears long [19]. Many authors report a particular toxicity with several severe cases after PDT. In our study, one patient had a severe side effect after PDT.

Today, there are several indications and various techniques to use PDT in the head and neck [8, 11, 21]. The low morbidity and functional disturbances that result from PDT offer many advantages in the treatment of recurrent cancer in particular.

The high cure rate obtain (70%) put in a prominent the importance of a meticulous follow up of patients treated for the head and neck cancer in order to detect new tumours at a curable stage, as Copper et al. have noted in 2007 [16]. In these conditions of a recurrent cancer of head and neck, in an early stage, PDT seems to be one of the best treatment possibilities.

PDT is a clinically and cost-effective treatment option for patients with recurrent or advanced head and neck cancer compared with palliative chemotherapy or extensive palliative surgery. PDT offers patients an unique chance of remission and increased life expectancy compared with palliative treatments [22-24]. The technique is simple, can commonly be carried out in outpatient clinics, and is highly acceptable to patients. It can be repeated to debulk large tumours progressively [25].

Competing interests: none

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