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(出國類別：進修)

頭頸部癌症之光動力治療

服務機關：臺大醫院耳鼻喉部
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內容摘要: 以傳統的治療方式治療頭頸部癌症，不僅治療的效果不理想，患者治療後的生活品質更是大爲降低。光動力治療是一項新的治療模式，它對於病人的外觀及呼吸吞嚥、發聲功能均不會影響，因此是治療頭頸部癌症一種很好的選擇。本人於民國九十一年六月負笈英國倫敦大學的國家醫學雷射中心進行光動力治療的基礎及臨床研究，在學術研究上回顧整理了雷射中心十年來頭頸部癌症光動力治療的長期結果，並已撰寫成論文發表。更重要的是本人在英國實際操作光動力治療治療了數名頭頸部癌症患者。這些寶貴的臨床經驗將是日後國內發展臨床光動力治療相當重要的基礎。

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摘要

以傳統的治療方式治療頭頸部癌症，不僅治療的效果不理想，患者治療後的生活品質更是大為降低。光動力治療是一項新的治療模式，它對於病人的外觀及呼吸吞嚥、發聲功能均不會影響，因此是治療頭頸部癌症一種很好的選擇。本人於民國九十一年六月負笈英國倫敦大學的國家醫學雷射中心進行光動力治療的基礎及臨床研究，在學術研究上回顧整理了雷射中心十年來頭頸部癌症光動力治療的長期結果，並已撰寫成論文發表。更重要的是本人在英國實際操作光動力治療治療了數名頭頸部癌症患者。這些寶貴的臨床經驗將是日後國內發展臨床光動力治療相當重要的基礎。

目次

一、目的

根據最近行政院衛生署所發表的統計數字顯示民國九十年全國每十萬人就有 148 人死於癌症，佔國人十大死亡原因的第一位，其中頭頸部癌症中的口腔癌與鼻咽癌則分佔男性十大癌症死亡原因的第五及第十位，且其死已率在近五年中有日益增加的趨勢。臨床上早期(stage I, II)之頭頸部癌症傳統的治療模式為手術，較晚期之癌症手術後尚需輔以放射治療。在某些特殊之部位如口咽或聲門癌手術會造成功能性的喪失，因此早期口咽癌或聲門癌之治療仍以放射治療為主。鼻咽癌是較為例外的，因為它對化學及放射治療極度敏感，因此不論期別均以放射治療或化學合併放射治療為主要的治療模式。然而，不論是手術或是放射治療都有其缺憾之處。不像身體其他部位的腫瘤可以被隱藏，頭頸部癌症手術後的傷痕或是切除後的組織缺損往往十分明顯而會造成患者心理上強烈的自卑感，有些患者甚至因此而甘脆逃避治療。放射治療的副作用與後遺症則更為可怕，不僅會破壞唾液腺造成吞嚥及進食的困難，長久之後還會有神經萎縮，骨頭缺氧壞死，甚至產生放射線引起之惡性腫瘤等後遺症。

有鑑於此，引進並開發新的、有效的頭頸部癌症治療模式，遂成為頭頸部癌症專家一項相當重要的課題。位於英國倫敦大學(University College London, UCL)的國家醫學雷射中心(National Medical Laser Centre, NMLC)使用光動力治療來治療癌症病患已經有十多年的歷史了，其在全世界臨床光動力治療的領域中一直居執牛耳的地位。光動力治療的機轉相當特殊，依據光感物質的不同而有不同的作用機轉。一般說來，在將光感物質送入腫瘤細胞後，光動力治療乃利用可見光或是雷射光照射腫瘤組織，活化光感物質產生單態氧(singlet oxygen)來破壞腫瘤細胞的粒腺體或是直接導致腫瘤細胞的凋亡。由於光感物質本身沒有毒性，必須在特定波長的可見光或是雷射光照射下才有生物活性，因此沒有照射到光的正常組織不會受到傷害，完全沒有傳統放射治療的副作用或後遺症，同時因為不須手術，所以也沒有美容外觀上的問題。

由於頭頸部的組織或是可以直接暴露在外(如口腔、口咽等部位)，或是經由簡單的內視鏡即可清楚到達(如鼻咽、喉頭、下咽等部位)，因此雷射光十分容易照射到腫瘤組織上，再加上國人頭頸部癌症的患者眾多，光動力治療應該是治療頭頸部癌症一項很好的選擇。為了引進這種新穎且效果極佳的新治療模式，本人遂於民國九十一年六月負笈英國倫敦大學的國家醫學雷射中心進行頭頸部癌症光動力治療的臨床及基礎研究。

二、過程

(一)國家醫學雷射中心簡介

國家醫學雷射中心是附屬於倫敦大學(UCL)外科(Academic Division of Surgical Specialties)的一個臨床轉譯研究(Clinical Translational Research)單位。它成立於 1984 年，現在的成員有共約 30 名的臨床研究員，研究護士，具有博士學位元的物理師，以及 Ph.D.學生，單位主持人是 Stephen G. Bown 教授。國家醫學雷射中心一直以來研究的重點是瞭解「光」與細胞及組織間的交互影響，同時應用這些交互影響的特性於人類疾病的診斷及治療上。中心內的研究內容大致可等分成實驗室研究及臨床研究兩部份。實驗室研究內容包括利用細胞培養及動物模式去探討雷射劑量學(laser dosimetry)，光傳輸系統(light delivery system)及光學光譜(optical spectroscopy)。臨床研究內容則包括 phase I, II 以及 III 的研究，目前主要的研究重心是放在光動力治療上面。國家醫學雷射中心與 UCL 醫院群中許多科部，包括顎面外科(maxillofacial surgery)，胃腸科(gastroenteroligy)，呼吸醫學科，泌尿科，血管外科，心臟內科，乳房外科，皮膚科，婦產科，放射診斷及放射治療科均有正在進行中的合作臨床研究計劃。Bown 教授一直很重視且強調的是將實驗室動物實驗的結果映証在病人身上，也就是前面所提的臨床轉譯研究。近 20 年來，雷射中心已經發表了近 300 篇的研究論文，有 30 個學生在雷射中心被授與學位(MD, MS 或 PhD)，共有來自 25 個不同國家的研床研究員曾在此進修或研究，Bown 教授則已被世界上 41 個不同國家邀請發表專題演講。

附錄 1 列出了目前正在國家醫學雷射中心進行中的研究活動。

(二)臨床研究

九十一年六月到達倫敦之後，與 Bown 教授就我在雷射中心的研究內容及方向作了詳細且深入的討論，同時並立即開始了臨床方面的工作。有別於其他進修國家的是英國由於實施公醫制度(National Health Service, NHS,類似我國的全民健保)，醫生的待遇普遍偏低，因此絕大多數的醫院都面臨醫師不足的窘境。同

時由於每年從世界各國到英國進修的醫生非常多，所以英國的醫政處(General Medical Council, GMC, 相當於我國的衛生署)規定外國醫生只要通過英文能力鑑定(IELTS)及本職學能資格鑑定，即可在某些特定的醫學中心，在某些特定的教授指導之下，執行醫療工作(也就是從事醫療行為而非僅是臨床觀察員)。由於我事前即已通過這些資格鑑定，因此被安排參與每週一次的頭頸部腫瘤門診，負責追蹤及診治光動力治療的病人。除了之外，每週尚有二日在 Mr. Colin Hopper (UCL 醫院及 Eastman Dental Institute 的 Senior Lecturer(相當於國內的副教授)，本身是 Maxillofacial Surgeon, 具有醫學及牙醫學雙學位，與雷射中心合作頭頸部癌症的光動力治療)的指導下進行頭頸部癌症光動力治療的實際治療工作。由於光動力治療在英國是已被核准的正統治療方式，幾乎全英國被認為適合或需要作光動力治療的病人都會被轉介到雷射中心來，因此單是頭頸部癌症每週就至少有一例光動力治療的病人。可惜的是光感藥物相當昂貴(一劑要價 8000 歐元)英國政府規定只有晚期頭頸部癌症患者予以給付，所以除非病人財力足以負擔或是私人保險可以核付，否則早期頭頸部癌症患者是無法享用光動力治療的(雖然早期癌症患者光動力治療的效果遠優於晚期癌症患者)，此點也大大地限制了光動力治療的普及化。幸而我在雷射中心有了這些寶貴的實際操作、執行光動力治療的經驗，相信對引進此治療回國應是有正面的幫助與意義。

除了規律的門診及治療工作外，個人對於光動力治療的長期效果也十分感興趣。雷射中心是全英國最早施行臨床光動力治療的中心，自 1991 年開始 Mr. Hopper 加入雷射中心並開始了頭頸部癌症的光動力治療。十多年來共計治療了近 400 例頭頸部癌症的患者，從早年第一代的光感物質 Photofrin 一直到近年使用最多的第二代光感物質 Foscan，確實累積了許多寶貴的臨床經驗與資訊。在 Mr. Hopper 的協助下，我利用公餘的時間將所有接受光動力治療病人的病歷調出來並仔細加以整理分析，同時回顧了文獻上所有關於頭頸部癌症光動力治療的論文而整理成一篇報告，已發表於最近一期的 Technology in Cancer Research and Treatment (附件 2)。除此之外，我還分析了自 1997 年 7 月至 2002 年 12 月 7 年

間 39 名接受介入性 (interstitial) 光動力治療的晚期頭頸部癌症患者的臨床資料，寫成論文並已於日前投稿寄出(附件 3)

(三)基礎研究

除了臨床上的研究工作之外，在雷射中心時我也作了一些光動力治療相關的基礎研究。由於向來一直認為光動力治療只能作用在光可穿透深度的腫瘤或組織，因此治療的深度並沒有辦法提昇(受限於光的穿透深度)。為了提高光動力治療的效率與成功率，我嚐試合併光動力治療與化學藥物治療，利用雷射中心已經設立好的動物肝臟模式與大腸癌動物模式進行實驗。由於一年的進修時間確實有限，因此這方面僅完成初步的結果，剩餘未完成的部份留待回國後繼續完成。

三、心得

(一)光動力治療是頭頸部癌症當然有效且值得推廣的治療方式。

頭頸部由於解剖位置的特殊，當發生癌症時，在治療上常常會因手術切除腫瘤及正常組織而導致患者外觀上產生明顯的醜形，即使能夠痊癒(cancer-free)，患者的自尊心及生活品質也會大打折扣。放射線治療對於早期頭頸部癌症雖然有效，但是其所引發之長期、不可逆的後遺症，對病人生活品質上所造成的傷害會更大。光動力治療被應用於治療頭頸部癌症雖然已有將近十年的歷史，但其療效及長期的效果卻尚未有定論。在還沒有到倫敦大學進修之前，我對光動力治療的療效雖感興趣，但仍有相當程度的懷疑。真正去了雷射中心以後，實地治療了幾個病人，也在門診追蹤了以前接受光動力治療的病人，我才相信光動力治療確實對頭頸部癌症具有相當不錯的療效。整體說來，早期頭頸部癌症患者接受光動力治療二年的 complete response rate 在 75%~100%(不同藥物，不同醫院有不同的結果)。最重要的是光動力治療即使失敗，病人仍能回頭去接受傳統的治療而不會影響其存活率，光動力治療後幾乎沒有疤痕，沒有長期的後遺症，對於頭頸部癌症的患者來說是一項很好的選擇。雖然光在組織的穿透能力有限，對於較大，較深的腫瘤我們仍能用 interstitial 的光動力治療來克服此點，並得到相當好的治療效果。

光動力治療的效果雖然不錯，但並不能完全取代傳統的治療模式。個人認為最重要的是謹慎、好好地選擇病人，對於嘴唇、軟顎、聲帶或是 field-cancerization 的患者，光動力治療不僅能夠保存病人的外觀，尚能維持功能上的完整，是一項非常好的治療模式。

(二)臨床轉譯(clinical translation)的研究方向

現式醫學的範疇十分廣泛，而研究的資源與經費卻十分有限，如何利用有限的資源去作最有效率的運用，是目前一個相當重要的課題。雷射中心自成立以來就一直定位在是一個臨床轉譯的研究中心。Bown 教授對於虛幻空泛的研究向來

沒有興趣，即使這些研究比較容易申請到經費。他認為研究的結果最終還是要迴饋到臨床病人身上，這樣的研究對病人最有直接的幫助，也才有意義，因此雷射中心所有的研究均以此概念為中心而衍生。個人認為一個醫學中心(例如台大醫學院區)包含的研究機構本身就相當多元化，有許多專長於基礎醫學(例如分子生物學，免疫學，微生物學等等)的研究學者，也有像我們這種具有臨床醫師身分的 physician scientist (PS)。一直以來相當困擾 PS 的一個問題是如何決定研究的方向與主題，因為如果作純基礎醫學的學術研究，則絕對無法跟專門的 scientist 競爭(時間，人力上)，如果作純臨床的研究(病人的資料分析、統計)則又無法與現今的學術主流接軌。去了一趟雷射中心之後，發覺像他們那樣的研究定位是一個值得學習的方向。因為畢竟只有我們醫生才瞭解什麼是病人真正的需要，根據病人的需要去設計並進行基礎研究，先從 in vitro 的細胞實驗開始，然後進到 in vivo 的動物實驗，最後將這些研究結果應用在臨床病人身上。這樣的一系列研究概念才是我們這些 PS 有真正著力點的地方。

(三)完善的準備是成功的要件

英國人作事很慢，在我們的觀點會覺得他們很沒有效率，反映在研究上，就是漫長的準備時間。剛到英國時由於進修期間僅有一年，因此急著想趕快開始進行實驗室的實驗工作，以免浪費有限的寶貴時間。孰料老闆對此完全不急，僅要求我作文獻的回顧並要我跟一些作純基礎研究的 Scientist 討論我想要作的實驗內容，同時要我先交一份研究計劃書給他。沒想到這份研究計劃書經過一再討論與修改，等到完成時已經是三個月之後的事情了。這三個月之間我們就計劃的內容，可行性、觀點……進行了多次的討論與推敲，最後才決定開始實行。也由於早已將實驗的內容作了完整的討論，因此當真正開始實驗之後，很快就有了結果。這樣的作研究方法跟我們在台灣有很大的不同，在台灣作研究大多是計劃畫寫得天花亂墜，先申請到錢再說，然後作實驗是且戰且走，往往最後作的東西與一開始時的計劃是完全不相關的，更有多數機會是浪費了很多錢之後才發現原先的計劃根本完全是從不通的。由此看來，英國人作事雖然慢，但卻不是沒有效率，

他們是把時間花在準備上，一但準備好了開始執行，其效率往往比我們這樣瞎打誤撞要好很多。

四、建議

對於院方的支援，使我能出國進修這一項對頭頸部癌症患者相當有意義的新治療方式，內心十分感激。唯一的建議是在出國的經費補助方面，由於倫敦的物價昂貴(平均是臺北的三~四倍)，因此院方給予的補助實在是不夠用。建議日後補助出國進修同仁應依據其所進修的地方之消費物價水準而進行調整補助金額，而非像目前美洲一律補助多少，歐洲一律補助多少這樣的方式，如此方能符合同仁真正的需要。

◎附錄 1

Current Research activities in the National Medical Laser Centre (NMLC)

The main research interest is **photodynamic therapy** (PDT, a technique for producing localised necrosis with light after prior administration of a photosensitising drug), in which the NMLC has an outstanding international reputation. The main attractions of PDT are: the effect is limited to tissues receiving an appropriate light dose (even after systemic administration of the photosensitising drug); connective tissues like collagen are largely unaffected (because there is no change in tissue temperature) so the mechanical integrity of hollow organs is preserved; there is no cumulative toxicity (so treatment can be applied more than once, even in tissues previously treated with radiotherapy); and there is excellent healing. An increasing number of pharmaceutical companies making photosensitiser drugs are negotiating research contracts with the NMLC. Research projects range from basic laboratory studies to phase I, II and III clinical trials.

Main cancer related PDT activities:

Hollow organs (direct or endoscopic light delivery)

Dysplasia, early and advanced cancer of the mouth (Mr Hopper). Over 250 patients treated, approaching a routine procedure.

Dysplasia and early cancer in Barrett's oesophagus (Dr Lovat). A programme in collaboration with the MRC in Cambridge (Dr Fitzgerald) to understand the biology of malignant change in Barrett's oesophagus and its response to PDT.

Dysplasia and early cancer in major airways (Dr George). A programme in collaboration with the MRC in Cambridge (Dr Rabbitts) to understand the molecular genetics of invasive change in severe dysplasia and to treat with PDT.

Localised cholangiocarcinoma (Dr Pereira). A few cases treated anecdotally, but national, multicentre trials currently being planned.

Solid organs (interstitial light delivery using fibres inserted through needles positioned percutaneously under image guidance with US, CT or MRI).

Cancer of the pancreas (localised but inoperable) (Dr Pereira, Prof Lees). Recent publication of **first clinical report** after several years of experimental work. Further clinical studies now being planned.

Cancer of the prostate recurring after radiotherapy (Mr Emberton, Dr Payne). Recent publication of the **first clinical report** after several years of experimental work. Further clinical studies now being planned.

Head & Neck cancer that has spread deep in the neck and under the skull base (Mr Hopper, Dr Jaeger). About 40 cases treated with good palliative effect.

Small, inoperable, peripheral lung cancers (inaccessible bronchoscopically) (Dr George). Shown to be safe in animal studies with clinical programme being planned.

A few cases of small, primary bone cancers have been treated after experiments showed that normal bone is remarkably resistant to PDT (Mr. Witt).

Main cancer related programmes using thermal lasers without photosensitising drugs

Interstitial Laser Photocoagulation (ILP). As for interstitial PDT, ILP involves light delivery using fibres inserted through needles positioned percutaneously under image guidance with US, CT or MRI. ILP destroys tissue by heat, so unlike PDT, collagen is damaged and the mechanical integrity of hollow organs is at risk. However, it is appropriate for ablating lesions in the centre of solid organs.

ILP for isolated hepatic metastases (Prof Lees). This was the first clinical application of ILP, although most treatments now use percutaneous, interstitial radiofrequency heating.

ILP for small breast cancers (Mr M. Keshtgar, Dr M. Hall-Craggs). This is a research programme treating small cancers with ILP and assessing the results with contrast enhanced MRI prior to conventional surgery to see if incompletely treated areas can be detected by the MRI. The ultimate aim is to use ILP as an alternative to lumpectomy.

We have also shown ILP to be an effective treatment for some benign lesions and are now using it for fibroadenomas of the breast (Mr M. Keshtgar), osteoid osteomas of bone (Mr J. Witt) and uterine fibroids (Mr A. Cutner).

Endoscopic applications of high power thermal lasers.

Endoscopic palliation of advanced, inoperable cancers of the oesophagus and rectum (Prof Bown, Dr Lovat). This is a well established service, but ongoing programmes are looking at combinations of laser therapy followed by palliative or radical radiotherapy and/or chemotherapy (Dr Tobias, Dr Blackman).

Endoscopic palliation of advanced bronchial cancers (Dr J.George, established service).

Optical diagnosis of dysplasia and cancer.

Elastic Scattering Spectroscopy (ESS) interrogates tissue with a short pulse of white light and then undertakes a spectral analysis of the light scattered back. It has the potential for immediate detection of cancer and dysplasia in a wide range of organs without the need to remove any tissue from the patient and without the need of a pathologist to interpret the result. Algorithms are being developed for automatic analysis of the optical spectra. It also has the potential to be developed for the instantaneous measurement of the concentration of drugs in living tissue. The NMLC has pioneered study of this technique (funded by the US Army) and has shown 89% sensitivity and 83% specificity for detecting dysplasia in Barrett's oesophagus as well as 84% sensitivity and 87% specificity for detecting metastatic cancer in excised axillary lymph nodes. With more data and refinements of the spectral analysis, these figures should improve further. Our further preliminary studies show promise for distinguishing malignant melanomas from benign pigmented skin lesions and for detecting dysplasia in the mouth and major airways.

Current experimental programmes related to cancer therapy

Development of techniques for monitoring PDT in real time (no macroscopic changes are visible until 1-2 days after PDT). Most work is focusing on measuring tissue oxygen levels by visible and infra-red spectroscopy using fibre optic probes that can

be applied to a tissue surface or interstitially. This is a major programme involving technical developments as well as *in vivo* studies.

PDT on normal rat gastrointestinal tract to find the best photosensitiser and treatment conditions for achieving mucosal necrosis without underlying muscle damage, as required for treating extended areas of abnormal mucosa (eg Barrett's oesophagus).

PDT on normal rat liver and colon to establish the relative importance of microvascular shutdown and cellular necrosis/apoptosis with different photosensitisers.

Studies on singlet oxygen (thought to be the cytotoxic intermediary in PDT).

In vitro studies on photochemical internalisation (PCI, see below).

Development of chemiluminescence as the light source for PDT

Development of light delivery devices for intraluminal and interstitial PDT.

Fundamentally new cancer research areas that could be developed in the NMLC:

Photochemical internalisation (PCI). The idea is to use PDT as a way of releasing other biologically active substances inside living cells. This could be used for anti cancer drugs or even as a way of introducing new genes into particular organs in the body. In vitro studies already suggest that this technique may be a way of killing chemotherapy resistant cells.

Interaction of PDT with angiogenesis. One of the mechanisms of PDT is to shut down small blood vessels (although larger vessels with adequate connective tissue in their walls maintain their mechanical integrity) and it is possible that PDT might be complementary to anti-angiogenesis drugs currently being developed and assessed.

The immunological effect of PDT. There is anecdotal evidence that PDT may give rise to a systemic immunological response, perhaps by the initial effect releasing previously hidden antigens. If this could be understood and exploited, it might have a role in treating micrometastatic disease.

PDT Research projects in the NMLC not related to cancer

Prevention of restenosis after balloon angioplasty (Dr J. McEwan, Mr C.Bishop). Publication of the **first clinical report** using adjuvant PDT to prevent restenosis after repeat angioplasty for recurrent femoral artery disease, after several years of experimental studies. A large, randomised clinical study is currently under way together with experimental work looking at combining PDT with arterial stents.

Treatment of menorrhagia by trans-cervical installation of photosensitiser and subsequent light delivery (Mr A Cutner). Experimental work is underway in rabbits, together with studies on light delivery devices using human hysterectomy specimens.

◎ 附錄 2

Clinical Outcomes of Photodynamic Therapy for Head-and-Neck Cancer

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Abstract

Head-and-neck cancers not only carry poor prognoses, but also reduced quality of life for the patients. Disease control is often achieved at the expense of substantial functional loss and disfigurement. Photodynamic therapy (PDT) is particularly well suited to the treatment of head-and-neck-tumours because it has little effect on underlying functional structures and has an excellent cosmetic outcome. Studies in the past decades have shown that PDT is of similar efficacy as traditional measures in the treatment of early-stage head-and-neck cancers with an overall response rate of 85%-100% with up to 75% of the complete responses sustained at 2 years after PDT. For advanced head-and-neck cancers, studies were also conducted to evaluate the palliative effects of PDT. Overall, 58%-70% palliative benefit can be observed in these patients. Using interstitial PDT, median survival of the patients with recurrent unresectable head-and-neck cancers can be improved to 14 months (cf. 226 days by using surface illumination PDT). PDT is thus a therapeutic option that may prove a useful addition to the armamentarium of the integrated head and neck oncology team.

Head-and-Neck Cancers- A Continuous Challenge to the Oncologists

Because of the complex regional anatomy, head-and-neck cancers constitute a unique category of human malignancy. Every year there are about 363.100 new cases of head-and-neck cancers over the world (81.600 cases in Europe)(1;2). The incidence varies considerably with different countries. For example, nasopharyngeal carcinoma (NPC) is common in Southeast China, Hong Kong, Singapore and Taiwan but is rare in the Western countries. Globally, the incidence of oral cavity cancer is highest in India and Southeast Asia whilst Western Europe has the highest incidence of oral cavity cancer in the Western countries(3;4). The mortality rate varies, on the other hand, with the site and stage of the primary tumours. Overall, thyroid cancers carry the best prognosis whilst oral cavity cancers have the worst prognosis(5;6). For oral cavity cancers, the probability of maintaining local control at two years for patients with T_1 or T_2 squamous cell carcinoma (SCC) is 75 – 85%(7). Although some early head-and-neck cancers are cured effectively, the overall outcome remains unsatisfactory. The overall survival rates have remained unchanged since 1974 at around 55% for white people and have declined slightly for blacks (down from 36% to 33%)(8-11).

Although chemotherapy plays an important role in the treatment of some head-and-neck cancers such as NPC(12;13), the mainstay of treatments for most of the head-and-neck cancers are surgery and

radiotherapy, either alone or in combination. Surgery is an effective measure for early stage cancers. However, because of the specialised function of the head-and-neck region, surgical resection, even of small volume tumours, can cause functional and aesthetic impairment leading to withdrawal and social isolation. For advanced tumours, major surgical ablation plus local or free-flap reconstruction leads to significant aesthetic and functional morbidity. Radiotherapy, although with less impact on the structural integrity, carries acute toxicities and long-term complications to the patients. Xerostomia, speech disorder, dysphagia, pain, osteoradionecrosis or depression develop long after completion of treatment, and greatly reduce the patients' quality of life(14-16). It might be possible to justify the sacrifice of life quality for patients if survival were improved. However, despite the advances in oncological disciplines during the last decades, about half of the head-and-neck cancer patients still succumb to their disease.

The management of head-and-neck cancers is further complicated by the occurrence of multiple primary malignancies. It is now accepted that the incidence of multiple primary SCC occurring in the upper aero-digestive tract can be as high as 20-30%(17;18). The pathogenesis is not well understood, but it is probably related to the effects of multiple carcinogens. Slaughter et al. had suggested the term "field cancerisation" to describe the situation where the entire region of upper aero-digestive tract mucosa is exposed to carcinogen, thereby increasing the risk of that tissue developing multiple independent pre-malignant and malignant areas(19). It is now known that sequential impairment of tumour suppressor genes and activation of oncogenes are also responsible for the pathogenesis of multiple primary head-and-neck cancers(20). It is also known that in the younger population or in patients with "condemned mucosa" the incidence of radiation-induced malignancies is greatly increased(21). Management of a second primary cancer within the previously operated or irradiated field is even more difficult. The difficulties associated with treating these tumours suggest a need for alternative treatments that are less destructive, repeatable and compatible with previous and subsequent radiotherapy and surgery.

Basic Mechanisms of Photodynamic Therapy

Photodynamic therapy (PDT) has been known for about a century but it wasn't until the mid-seventies that there was a real breakthrough. Dougherty and his colleagues reported a cure of 48% of rats and mice with subcutaneously implanted tumours treated with haematoporphyrin derivative (HpD) mediated PDT(22). Three years later, the same group published highly encouraging results of the first clinical trial on 25 patients with various types of tumours, mainly metastatic, effectively inactivated by PDT(23). PDT is a site-specific, non-thermal, minimally invasive procedure. It requires a photoactive substance (photosensitiser) to absorb light (photon) of a specific wavelength matching the absorption characteristics of the photosensitising agent. On illumination, the photosensitiser is activated from a stable electronic ground state, to a short-lived, highly unstable excited state, then to a metastable triplet state. The triplet state of the photosensitiser has a relative long lifetime and can undergo either electron transfer to a nearby suitable molecule (e.g. membrane lipid) (type I reaction) or energy transfer to the surrounding molecular oxygen (type II reaction)(24). Hydrogen peroxide and other superoxide radical anions are produced directly from the type I photodynamic reaction whilst the

non-radical, highly reactive singlet oxygen species are produced through the type II photodynamic reaction. Both reactions may occur simultaneously and are responsible for the photoinactivation effects of PDT. However, it is generally accepted that the type II photodynamic reaction is probably the main mechanism of PDT-induced cell death. In addition to the 2 types of photodynamic reactions, vascular shutdown to the tumour as well as PDT-induced immunological responses are also involved in the tumouricidal effects of PDT(25).

Advantage of PDT over Conventional Measures for Head-and-Neck Cancers

Most of the photosensitisers are selectively retained by the cancer cells due to unknown mechanisms. Accordingly, in clinical practice, the photosensitiser is administered first and then illumination is carried out when a differential in photosensitiser concentration between the tumour tissue and adjacent normal tissue has developed. This protocol encourages neoplastic tissue necroses with some preservation of the normal tissue. Because PDT is a non-thermal reaction, the necrosis is localised and healing takes place with little scarring, and good preservation of function(26;27). Surgery, radiotherapy, or chemotherapy does not preclude the use of PDT nor will PDT compromise the subsequent use of any other treatment(28). Unlike ionising irradiation, PDT is repeatable without cumulative tissue toxicity(29). Because of these characteristics, PDT is an ideal option in the treatment of head-and-neck cancers.

Photosensitisers for Clinical Head-and-Neck Cancer Treatment

To verify the safety and efficacy of PDT in the treatment of head-and-neck cancers, many clinical studies have been performed during the last 2 decades. Although new photosensitisers have been synthesized, only a few of them have been used in clinical head-and-neck cancer patients. **Table I** compares the three most commonly used sensitisers. Porfimer sodium (Photofrin) is one of the first generation photosensitisers and belongs to the HpDs. It is probably the most extensively studied and clinically used photosensitiser. It is also the first photosensitiser to receive regulatory approval. Over 4000 patients with various cancers have been treated with Photofrin to date(30). Photofrin absorbs light maximally at about 400 nm, however, the absorption band that is used clinically in the red at about 630 nm is relatively weak. Therefore, the depth of effect for photofrin is limited to about 0.5 cm. Clinically, the major drawback of photofrin is the prolonged skin photosensitivity, sometimes longer than 4-6 weeks after sensitisation(31). The second photosensitiser used in head-and-neck oncology is 5-aminolaevulinic acid (ALA). ALA is a naturally occurring photosensitising precursor which is metabolised to a photoactive endogenous intermediate substance, protoporphyrin IX (PPIX), in the mitochondria matrix(32). ALA can be given topically, orally or intravenously and its active metabolite, PPIX, can be activated by red, green, and even blue light. There are great variations in the amount of PPIX accumulated following ALA administration in different organs and tissues. A notably higher level of ALA induced PPIX was found in the epithelial lining tissues- urothelium, endometrium, and mucosa of the hollow organs of the gastrointestinal tract(33-35) than in the underlying submucosa and muscle layers. The specific distribution of ALA makes it a good candidate for the treatment of superficial, mucosa lesions. But it is also because of this limited tissue penetration (< 0.2 cm) that makes ALA not

suitable for treating deep, bulky tumours. Meta tetrahydroxyphenyl chlorin (mTHPC, temoporfin, Foscan) is the third photosensitiser that is used in clinical head-and-neck cancer patients. Foscan has a strong absorption peak in the red part of the spectrum at 652 nm, which gives better tissue penetration than at the 630 nm required for photofrin(36). Reflecting to the depth of treatment, Foscan-PDT-induced necrosis can reach to about 1 cm in depth. Foscan is also a much more effective generator of singlet oxygen species than HpD. So the light doses used in Foscan-PDT are far less than the first generation photosensitisers and the treatment time can be shortened to only a few minutes. Another advantage of Foscan-PDT is skin photosensitivity to bright light lasts for only about 2-3 weeks, up to a maximum of about a month.

The Evolution of Head-and-Neck Cancer PDT

The clinical reports of implementing PDT in the treatment of head-and-neck cancers can be traced back to about 20 years ago and the whole span can be divided into halves. Before 1994, all the studies were performed using the first generation photosensitisers, e.g. HpD or Photofrin. The studies established that PDT could be an important adjuvant treatment modality for head-and-neck cancers. It also laid the foundation of future development of clinical PDT. After 1994, PDT has got regulatory approval and several second-generation photosensitisers have been developed and used in pre-clinical and clinical trials. Unfortunately because of the financial problem and collapse of the manufacturer of Foscan, the most potent photosensitiser for head-and-neck cancer treatment to date, the development of head-and-neck PDT was slowed down. Recently, Foscan has been back to the market again and many clinical trial results using Foscan-PDT to treat head-and-neck cancers will soon be published.

PDT with the First Generation Photosensitisers (Table II)

In 1985, Schuller et al. reported their results of HpD-PDT on 24 patients with recurrent or metastatic head-and-neck cancers(37). All tumours responded to PDT albeit the durations were short. Using Photofrin as a photosensitiser, Keller et al. treated 31 patients with PDT and reported all 3 early stage oral cavity cancers in their series achieved complete responses (CR) whilst bulky tumours or neck metastases responded poorly(38). Using the same photosensitiser, Grossweiner et al. treated 9 patients with early recurrent oral cavity and pharynx cancers. Eight patients had CR whilst the remaining one patient had partial response (PR)(39). Freche and DeCorbiere treated 32 patients with T1 glottic carcinomas with HpD or Photofrin and achieved a 78% CR rate with 12- to 48-month follow-up(40). Zhao et al. treated 50 patients with lip cancer using HpD-PDT and achieved a 100% cure rate(41). They also treated 31 patients with various head-and-neck cancers with combined PDT and radiotherapy and achieved a 100% CR rate. The authors thus suggested that PDT may enhance the effect of radiotherapy(42). Feyh et al. treated 30 patients with T1 malignancies of the face and oropharynx. Seven of the 8 oral cavity tumours in their series had CR(43). Wenig et al. reported on 26 treated patients with early recurrent SCC. Histological CR was noted in 77% of their patients for periods up to 48 months(44). Gluckman reported his 5-year experience of Photofrin-PDT on 41 head-and-neck cancer patients. Superficial early (T1 or T2) cancers of the oral cavity and oropharynx were the easiest to treat. Eleven of 13 such tumours had CR. However, for tumours of other head-and-neck sub-sites

and advanced recurrent tumours, the results were disappointing(45). Grant et al. treated 11 patients with "field cancerisation" and early oral cavity cancers with Photofrin-PDT. Ten of the 11 patients showed a CR after 8 weeks and no patient had evidence of recurrent invasive carcinoma in the treated area at the last follow-up(46). The largest series of HpD- and Photofrin-based PDT for head-and-neck cancer treatment comes from the works of Biel. He reported treating 107 head-and-neck cancer patients, including 33 laryngeal, 32 oral, nasal, or nasopharyngeal, 13 recurrent or primary T2 or T3, 12 recurrent but resectable, 4 recurrent unresectable tumours and some melanomas and sarcomas, in a 7-year span(47-51). Overall, more than 90% of the early-stage tumours had CR (mean follow-up 37-44 months). Biel also published the first report of using intra-operative PDT for recurrent but resectable tumours(52). Salvage operation was performed first in those patients and PDT was then used to eradicate the microscopic disease. Among the 12 patients he treated, 7 were disease-free for a mean follow-up of 44 months. Four of the remaining 5 patients developed distant metastasis and the other one had a real in-field local failure. Tong et al. treated 12 recurrent NPC patients with HpD-PDT(53). All 12 recurrent tumours showed response to the treatment. Of the 8 patients treated with curative intent, 3 remained disease-free at 9-12 months after a single treatment. In a recent paper, Schweitzer et al. reported their long-term experience with Photofrin-PDT in the treatment of early-stage (Cis-T2) oral, oropharyngeal and laryngeal cancers(54). Sixteen of the 20 patients had CR and the response sustained for up to 9 years. Overall, Patients with early-stage cancers or early recurrences (Cis, T1 and early T2) tend to have a very good response to HpD or Photofrin-PDT. About 85-100% of the tumours obtained a complete clinical response after one PDT treatment. Phototoxicity is the most commonly noticed side effect. However, results of treating bulky tumours and neck metastases were disappointing.

PDT with the Second Generation Photosensitisers (Table III)

Grant et el. published the first report of using ALA-PDT in the treatment of oral cavity cancers(55). Three of the four tumours showed marked necrosis after PDT treatment. Fan et al. continued the study and implemented ALA-PDT to treat 18 patients with premalignant and malignant lesions of the oral cavity(56). All 12 patients with dysplasia improved after PDT whilst only 2/6 patients with carcinomas gained CR. They also studied the depth of necrosis produced by ALA-PDT. Although complete epithelial necrosis was present in all cases, the depth of necrosis by ALA-PDT was only 0.1 to 1.3 mm(56). Another study by Sieron et al. also showed that ALA-PDT was not efficient enough to treat head-and-neck SCCs(57). In general, ALA-PDT is good for head-and-neck premalignant lesions (over 80% CR rate) but not efficient enough to eradicate malignant tumours.

Foscan is so far the most potent licensed photosensitiser for PDT. The maximum depth of necrosis produced by Foscan-PDT can be up to 1 cm. Fan et al. used Foscan-PDT to treat 20 patients with premalignant or malignant tumours in the mouth. CR was achieved in 9/12 SCC patients(58). Kubler et al. treated 25 patients with early stage (Tis-T2) lip cancers and reported a 96% CR rate at 3 months(59). Only 2 of the complete responders recurred (one 4 months and the other one 18 months after PDT) during the follow-up. A large-scale multi-centre study using Foscan-PDT for early stage (Tis, T1 and early T2) oral cancers has been completed recently(60). The CR rate at 2 years was 75%

after one PDT treatment. For those who failed the primary PDT treatments, "salvage" measures, including re-PDT, surgery or radiotherapy, were used and CR could be achieved in 8/13 patients. Savary et al. treated 25 synchronous or metachronous early second primary head-and-neck SCC patients (total 33 tumours) with Foscan-PDT(61). CR was observed in 85% (28/33) of the tumours (median follow-up 14 months). Tan treated 41 "early" recurrent or second primary oral cancer patients and achieved an 89% CR rate if the tumour size was no bigger than 2 cm(62). However, if the tumour size was bigger than 3 cm, the CR rate dropped to 29%. To assess the efficacy of Foscan-PDT in the palliative treatment of head-and-neck cancers, another multi-centre study was performed(63). A total of 64 recurrent or second primary head-and-neck cancer patients who were not suitable or had exhausted traditional salvage modalities were recruited into the study. The median survival of the patients after PDT was 226 days. Fifty-eight percent overall palliative benefit was achieved. The limitation of surface-illumination PDT is the penetration of light in tissues. Although early-stage superficial tumours are cured effectively, the results of treating large, bulky tumours are disappointing. To overcome the limitation of PDT, Lou et al. implemented interstitial PDT to treat recurrent, unresectable head-and-neck cancers(64). The overall median survival of the patients was 14 months whilst 72% overall palliative benefit was achieved. The local control rate at 12 months was 41%. The advantages of Foscan-PDT, compared with Photofrin-PDT, are deeper tissue penetration and tumour necrosis, shorter treatment time and less phototoxicity. It is a safe and effective measure for both early-stage oral cavity cancers and recurrent unresectable head-and-neck cancers.

Conclusion

Although it is very difficult to treat head-and-neck cancers satisfactorily, PDT seems to be particularly suited for these tumours because it has little effect on underlying functional structures and has an excellent cosmetic outcome. Studies in the past have confirmed that PDT is a safe and effective means in the treatment of head-and-neck cancers. Recent developments in biochemical and molecular technology have improved the specificity and efficacy of photosensitisers. Treatment time is greatly reduced whilst depth of tumour necrosis is greatly increased. Improvement in the light delivery system and implementing interstitial treatment into PDT has extended the indication of PDT from surface, superficial tumours to deep-seated, bulky tumours. PDT is a therapeutic option that may prove a useful addition to the armamentarium of the integrated head and neck oncology team.

Reference List

1. **Black RJ, Bray F, Ferlay J, Parkin DM.** Cancer Incidence and Mortality in the European Union: Cancer Registry Data and Estimates of National Incidence for 1990. *European Journal of Cancer* 1997; 33: 1075-107.

2. **Parker SL, Tong T, Bolden S, Wingo PA.** Cancer statistics, 1997. *CA Cancer J Clin* 47: 5-27.

3. **Black RJ, Bray F, Ferlay J, Parkin DM.** Cancer Incidence and Mortality in the European Union: Cancer Registry Data and Estimates of National Incidence for 1990. *European Journal*

of Cancer 1997; 33: 1075-107.

4. **Parker SL, Tong T, Bolden S, Wingo PA.** Cancer statistics, 1997. *CA Cancer J Clin* 47: 5-27.

5. **Black RJ, Bray F, Ferlay J, Parkin DM.** Cancer Incidence and Mortality in the European Union: Cancer Registry Data and Estimates of National Incidence for 1990. *European Journal of Cancer* 1997; 33: 1075-107.

6. **Pisani P, Parkin DM, Bray F, Ferlay J.** Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999; 83: 18-29.

7. **Hong A, Saunders MI, Dische S et al.** An audit of head and neck cancer treatment in a Regional Centre for Radiotherapy and Oncology. *Clin Oncol (R Coll Radiol)* 1990; 2: 130-7.

8. **Blair EA, Callender DL.** Head and neck cancer. The problem. *Clin Plast Surg* 1994; 21: 1-7.

9. **Parker SL, Tong T, Bolden S, Wingo PA.** Cancer statistics, 1997. *CA Cancer J Clin* 47: 5-27.

10. **Pisani P, Parkin DM, Bray F, Ferlay J.** Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999; 83: 18-29.

11. **Wildt J, Bjerrum P, Elbrond O.** Squamous cell carcinoma of the oral cavity: a retrospective analysis of treatment and prognosis. *Clin Otolaryngol* 1989; 14: 107-13.

12. **Posner MR, Colevas AD, Tishler RB.** The role of induction chemotherapy in the curative treatment of squamous cell cancer of the head and neck. *Semin Oncol* 2000; 27: 13-24.

13. **Hong RL, Ting LL, Ko JY et al.** Induction chemotherapy with mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin followed by radiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma. *J Clin Oncol* 2001; 19: 4305-13.

14. **Bjordal K, Kaasa S, Mastekaasa A.** Quality of life in patients treated for head and neck cancer: a follow-up study 7 to 11 years after radiotherapy. *Int J Radiat Oncol Biol Phys* 1994; 28: 847-56.

15. **Hammerlid E, Taft C.** Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. *Br J Cancer* 2001; 84: 149-56.

16. **Nguyen NP, Sallah S, Karlsson U, Antoine JE.** Combined chemotherapy and radiation therapy for head and neck malignancies: quality of life issues. *Cancer* 2002; 94: 1131-41.

17. **Savary M, Monnier P, Pasche R, Brossard E, Pasche P, Lang F.** Multiple primary malignancies. *Advances in Oto-Rhino-Laryngology* 1991; 46: 165-75.

18. **Gluckman JL, Crissman JD.** Survival rates in 548 patients with multiple neoplasms of the upper aerodigestive tract. *The Laryngoscope* 1983; 93: 71-4.

19. **Slaughter DP, SH, SW.** 'Field cancerisation' in oral stratified squamous epithelium. *Cancer* 1953; 6: 963-8.

20. **Forastiere A, Koch W, Trotti A, Sidransky D.** Head and neck cancer. *N Engl J Med* 2001; 345: 1890-900.

21. **Patel SG, See AC, Williamson PA, Archer DJ, Evans PH.** Radiation induced sarcoma of the head and neck. *Head Neck* 1999; 21: 346-54.

22. **Dougherty TJ, Grindey GB, Fiel R, Weishaupt KR, Boyle DG.** Photoradiation therapy. II. Cure of animal tumors with hematoporphyrin and light. *J Natl Cancer Inst* 1975; 55: 115-21.

23. **Dougherty TJ, Kaufman JE, Goldfarb A, Weishaupt KR, Boyle D, Mittleman A.** Photoradiation therapy for the treatment of malignant tumors. *Cancer Res* 1978; 38: 2628-35.

24. **Henderson BW, Dougherty TJ.** How does photodynamic therapy work? *Photochem Photobiol* 1992; 55: 145-57.

25. **Dougherty TJ, Gomer CJ, Henderson BW et al.** Photodynamic therapy. *JNCI Cancer Spectrum* 1998; 90: 889-905.

26. **Hopper C.** Photodynamic therapy: a clinical reality in the treatment of cancer. *Lancet Oncol* 2000; 1: 212-9.

27. **Barr H, Tralau CJ, Boulos PB, MacRobert AJ, Tilly R, Bown SG.** The contrasting mechanisms of colonic collagen damage between photodynamic therapy and thermal injury. *Photochem Photobiol* 1987; 46: 795-800.

28. **Hornung R, Walt H, Crompton NE 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: 569-74.

29. **Biel MA.** Photodynamic therapy and the treatment of head and neck neoplasia. *Laryngoscope* 1998; 108: 1259-68.

30. **Biel MA.** Photodynamic therapy and the treatment of head and neck neoplasia. *Laryngoscope* 1998; 108: 1259-68.

31. **Grant WE, Speight PM, Hopper C, Bown SG.** Photodynamic therapy: An effective, but non-selective treatment for superficial cancers of the oral cavity. *International Journal of*

Cancer 1997; 71: 937-42.

32. **Kennedy JC, Marcus SL, Pottier RH.** Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results. *J Clin Laser Med Surg* 1996; 14: 289-304.

33. **Bedwell J, Macrobert AJ, Phillips D, Bown SG.** Fluorescence Distribution and Photodynamic Effect of Ala- Induced Pp-Ix in the Dmh Rat Colonic Tumor-Model. *British Journal of Cancer* 1992; 65: 818-24.

34. **Loh CS, Vernon D, MacRobert AJ, Bedwell J, Bown SG, Brown SB.** Endogenous porphyrin distribution induced by 5-aminolaevulinic acid in the tissue layers of the gastrointestinal tract. *J Photochem Photobiol B* 1993; 20: 47-54.

35. **Chang SC, MacRobert AJ, Bown SG.** Biodistribution of protoporphyrin IX in rat urinary bladder after intravesical instillation of 5-aminolevulinic acid. *J Urol* 1996; 155: 1744-8.

36. **Ma L, Moan J, Berg K.** Evaluation of a new photosensitizer, meso-tetra-hydroxyphenyl-chlorin, for use in photodynamic therapy: a comparison of its photobiological properties with those of two other photosensitizers. *Int J Cancer* 1994; 57: 883-8.

37. **Schuller DE, McCaughan JS, Rock RP.** Photodynamic therapy in head and neck cancer. *Arch Otolaryngol* 1985; 111: 351-5.

38. **Keller GS, Doiron DR, Fisher GU.** Photodynamic therapy in otolaryngology--head and neck surgery. *Arch Otolaryngol* 1985; 111: 758-61.

39. **Grossweiner LI, Hill JH, Lobraico RV.** Photodynamic therapy of head and neck squamous cell carcinoma: optical dosimetry and clinical trial. *Photochem Photobiol* 1987; 46: 911-7.

40. **Freche C, De C.** Use of photodynamic therapy in the treatment of vocal cord carcinoma. *J Photochem Photobiol B* 1990; 6: 291-6.

41. **Zhao FY, Zhang KH, Ma DQ et al.** Treatment of 570 cases of oral squamous cell carcinoma. *Ann Acad Med Singapore* 1989; 18: 533-6.

42. **Zhao FY, Zhang KH, Ma DQ et al.** Treatment of 570 cases of oral squamous cell carcinoma. *Ann Acad Med Singapore* 1989; 18: 533-6.

43. **Feyh J, Goetz A, Muller W, Konigsberger R, Kastenbauer E.** Photodynamic therapy in head and neck surgery. *J Photochem Photobiol B* 1990; 7: 353-8.

44. **Wenig BL, Kurtzman DM, Grossweiner LI et al.** Photodynamic therapy in the treatment of

squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1990; 116: 1267-70.

45. **Gluckman JL.** Hematoporphyrin photodynamic therapy: is there truly a future in head and neck oncology? Reflections on a 5-year experience. *Laryngoscope* 1991; 101: 36-42.

46. **Grant WE, Hopper C, Speight PM, Macrobert AJ, Bown SG.** Photodynamic therapy of malignant and premalignant lesions in patients with 'field cancerization' of the oral cavity. *J Laryngol Otol* 1993; 107: 1140-5.

47. **Biel MA.** Photodynamic therapy and the treatment of neoplastic diseases of the larynx. *Laryngoscope* 1994; 104: 399-403.

48. **Biel MA.** Photodynamic therapy as an adjuvant intraoperative treatment of recurrent head and neck carcinomas. *Arch Otolaryngol Head Neck Surg* 1996; 122: 1261-5.

49. **Biel MA.** Photodynamic therapy and the treatment of head and neck cancers. *J Clin Laser Med Surg* 1996; 14: 239-44.

50. **Biel MA.** Photodynamic therapy and the treatment of head and neck neoplasia. *Laryngoscope* 1998; 108: 1259-68.

51. **Biel MA.** Photodynamic therapy of head and neck cancers. *Semin Surg Oncol* 1995; 11: 355-9.

52. **Biel MA.** Photodynamic therapy as an adjuvant intraoperative treatment of recurrent head and neck carcinomas. *Arch Otolaryngol Head Neck Surg* 1996; 122: 1261-5.

53. **Tong MC, van H, Woo JK.** Preliminary results of photodynamic therapy for recurrent nasopharyngeal carcinoma. *Eur Arch Otorhinolaryngol* 1996; 253: 189-92.

54. **Schweitzer VG.** PHOTOFRIN-mediated photodynamic therapy for treatment of early stage oral cavity and laryngeal malignancies. *Lasers Surg Med* 2001; 29: 305-13.

55. **Grant WE, Hopper C, MacRobert AJ, Speight PM, Bown SG.** Photodynamic therapy of oral cancer: photosensitisation with systemic aminolaevulinic acid. *Lancet* 1993; 342: 147-8.

56. **Fan KFM, Hopper C, Speight PM, Buonaccorsi G, MacRobert AJ, Bown SG.** Photodynamic therapy using 5-aminolevulinic acid for premalignant and malignant lesions of the oral cavity. *Cancer* 1996; 78: 1374-83.

57. **Sieron A, Namyslowski G, Misiolek M, Adamek M, Kawczyk K.** Photodynamic therapy of premalignant lesions and local recurrence of laryngeal and hypopharyngeal cancers. *Eur Arch Otorhinolaryngol* 2001; 258: 349-52.

58. **Fan KFM, Hopper C, Speight PM, Buonaccorsi GA, Bown SG.** Photodynamic therapy using mTHPC for malignant disease in the oral cavity. *International Journal of Cancer* 1997; 73: 25-32.

59. **Kubler AC, de Carpentier J, Hopper C, Leonard AG, Putnam G.** Treatment of squamous cell carcinoma of the lip using Foscan- mediated Photodynamic Therapy. *International Journal of Oral and Maxillofacial Surgery* 2001; 30: 504-9.

60. Hopper, C. Photodynamic therapy with Foscan (temoporfin) in primary squamous cell carcinoma of the head and neck. 2000. Proceedings Fifth International Congress on Head and Neck Oncology; San Francisco, USA.

Ref Type: Conference Proceeding

61. **Savary JF, Monnier P, Fontolliet C et al.** Photodynamic therapy for early squamous cell carcinomas of the esophagus, bronchi, and mouth with m-tetra (hydroxyphenyl) chlorin. *Arch Otolaryngol Head Neck Surg* 1997; 123: 162-8.

62. Tan IB. Foscan-mediated photodynamic therapy (Foscan-PDT) in recurrent and second primary oral cavity cancers. 2003.

Ref Type: Unpublished Work

63. Wenig, B. L., D'Cruz A, Iqbal A, and Bryce RP. Foscan-mediated photodynamic therapy (Foscan PDT) in the palliative treatment of advanced head and neck cancer. 19 (abstr165). 2000. Proc Am Soc Clin Oncol.

Ref Type: Conference Proceeding

64. Lou, P. J., Jager, H. R., Theodossy, T, Jones, L, Bown, S. G., and Hopper, C. Interstitial photodynamic therapy as a salvage treatment for recurrent head-and-neck cancers. 2003.

Ref Type: Unpublished Work

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Table I. The Most Commonly Used Photosensitisers in Head-and-Neck PDT

Sensitiser	**Photofrin**	**ALA**	**Foscan**
Drug Dose	1.5-5 mg IV	60 mg/kg Oral	0.1-0.3 mg/kg IV
Drug-Light Interval	24-72 hrs	3-6 hrs	36-168 hrs
Light Wavelength	630 nm	635 nm	652 nm
Light Dose	100 J/cm^2	100 J/cm^2	20 J/cm^2

Table II. Selected Reports of PDT with the First Generation Photosensitisers

Reference	Tumour site	N	Photosensitiser	Main results
Schuller et al.[37]	Head-and-neck	24	HpD	All tumours responded to PDT
Keller et al.[38]	Oral cavity	31	Photofrin	Early-stage tumours: CR 100% (3/3)
Grossweiner et al.[39]	Oral cavity and pharynx	9	Photofrin	CR: 89% (8/9), PR: 11% (1/9)
Freche and DeCorbiere[40]	T1 Glottic	32	HpD or Photofrin	CR: 78% (follow-up 12-48 months)
Zhao et al.[41,42]	Lip	50	HpD	CR: 100%
	Head-and-neck	31	HpD + RT	CR: 100%
Feyh et al.[43]	T1 Face and oropharynx	30	Photosan III	CR: 88% (7/8) of T1 oral cavity tumours
Wenig et al.[44]	T1 various sites	26	Photofrin	CR: 77% for up to 48 months
Gluckman[45]	Head-and-neck	41	Photofrin	T1 + T2 oral cavity and oropharynx tumours: CR 85% (11/13)
Grant et al.[46]	Oral cavity	11	Photofrin	CR: 90% (10/11)
Biel[30, 47-52]	Head-and-neck	107	Photofrin	T1 larynx: CR 21/21 T2 larynx: CR 4/5 T1, superficial T2+T3 oral cavity, nasal, nasopharyngeal: CR: 32/32
			Intra-operative PDT	Recurrent but respectable tumours: NER 7/12 (follow-up 44 months)
Tong et al[53]	Nasopharynx	12	HpD	NER 3/8 patients with curative intent
Schweitzer et al.[54]	Cis-T2 various sites	20	Photofrin	Oral cavity and oropharynx: CR 80% (8/10) Larynx: CR 80% (8/10)

CR: complete response, NER: no evidence of recurrence, PR: partial response

Table III. Selected Trials of PDT with the Second Generation Photosensitisers

Reference	Tumour site	N	Photosensitiser	Main results
Grant et al.[55]	Oral cavity	4	ALA	Tumour necrosis in 3/4 carcinomas
Fan et al.[56]	Oral cavity	18	ALA	12/12 dysplasia improved
	(field-change)			CR: 2/6 carcinomas
Sieron et al.[57]	Larynx and	5	ALA	CR: 4/5 dysplasia
	hypopharynx			PR: 5/5 carcinomas
Fan et al.[58]	Oral cavity	20	Foscan	CR: 6/6 up to T3 carcinomas
	(field-change)			3/6 T4 carcinomas
Kubler et al.[59]	Lip (Tis-T2)	25	Foscan	CR: 96% (24/25) at 3mo
				2 recurrences 4 and 18 mo after PDT
Hopper et al.[60]	Oral cavity	108	Foscan	82% CR after 1 year, 75% CR after 2
	(Tis-T2)			years
Savary et al.[61]	Head-and-neck	33	Foscan	85% CR (F/U 14 mo)
Tan et al.[52]	Oral cavity	41	Foscan	89% CR if tumour < 2cm
				29% CR if tumour > 3 cm
Wenig et al.[63]	Head-and-neck	64	Foscan	CR: 16%, median survival: 226 days
				58% overall palliative benefit
Lou et al.[64]	Head-and-neck	39	Foscan	Response rate: 89% (14% CR)
	(recurrent,		(interstitial)	Overall median survival: 14 mo
	unresectable)			72% overall palliative benefit

CR: complete response, F/U: follow up, PR: partial response

◎ 附錄 3

Interstitial Photodynamic Therapy as Salvage Treatment for Recurrent Head and Neck Cancer

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Abstract
Objective: To assess the safety and efficacy of interstitial photodynamic therapy (IPDT) for advanced head and neck cancers.
Design: Phase I-II study.
Setting: Multidisciplinary oncology clinic at the University College London Hospitals.
Participants: Patients with persistent or recurrent head and neck cancer unsuitable for further treatment with surgery, radiotherapy or chemotherapy, who were referred for "last hope" salvage treatment.
Results: 45 patients were treated and follow up was available on 39. Nine achieved a complete response of whom five are alive and free of disease 10-60 months later. Symptomatic relief (mainly for bleeding, pain or tumour debulking) was achieved in a further 23. The median survival (Kaplan-Meier) was 16 months for the 32 responders but only 1 month for the seven non-responders. The only serious complication was a carotid blow out 2 weeks after PDT.
Conclusions: IPDT provides worthwhile palliation with few complications and occasional long term survivors for otherwise untreatable advanced head and neck cancers. It is a treatment option worth adding to those available to integrated head and neck oncology teams.

Introduction
The treatment of head and neck cancer continues to pose a major clinical challenge. Although some early cancers can be cured, the overall survival rates have remained unchanged for several decades.[1] Thirty to forty percent of patients with head and neck cancer have persistent or recurrent locoregional disease after completion of definitive treatment. In the majority, surgical salvage is either not feasible or carries a high risk of complications.[2] Similarly, further radiotherapy is often impossible as surrounding tissues will already have received the maximum tolerable dose of ionising radiation.[3,4] Only a very small portion of these patients are long-term survivors.

Photodynamic therapy (PDT) is a site-specific tumour treatment involving the administration of a photosensitiser followed by focal activation in the presence of oxygen using light of a wavelength matched to an absorption peak of the photosensitiser.[5] For cancers of the oral cavity, the function and appearance of the mouth can be preserved without sacrificing the efficacy of tumour control.[6,7] PDT does not have the cumulative toxicity associated with ionising radiation and can be applied safely to previously irradiated tissues. Thus, it has considerable potential for patients with locally persistent or recurrent disease after surgery or radiotherapy.

PDT is usually undertaken with external illumination of the target tissue, but larger lesions in surgically inaccessible sites can be treated using interstitial therapy, in which multiple laser fibres are inserted directly into tumours through needles positioned under image guidance.[8] In this paper, we report the first phase I-II study to assess the safety and efficacy of interstitial PDT (IPDT) as a salvage treatment for recurrent head and neck cancers.

Materials and Methods.
Patients
Patients with biopsy confirmed persistent or recurrent head and neck cancers were recruited from the multidisciplinary oncology clinic at the University College London Hospitals. These tumours were

either considered unresectable or the patients were not suitable for further surgery. Some patients already had complications from prior radiotherapy and none were suitable for further irradiation. All were regarded as having a poor prognosis. All patients underwent either computerised tomography (CT) or magnetic resonance imaging (MRI) to assess the extent of disease. The experimental nature of the treatment was explained and written consent was obtained. The study was approved by the ethics committee of the University College London Hospitals, although during the course of the study, the photosensitising drug used was approved by the European Medicines Evaluation Agency for surface illumination PDT in this group of patients.

Interstitial Photodynamic Therapy

Patients were sensitised with 0.15 mg/kg intravenous meso-tetrahydroxyphenyl chlorin (mTHPC, Foscan®, Biolitec Pharmaceuticals Ltd, Germany) and were treated 4 days later. The light source was a diode laser (Diomed Ltd, Cambridge, or Ceramoptec Gmbh, Germany, wavelength 652 nm) with the primary beam feeding into a beam splitter to produce four treatment fibres (core diameter 0.4 mm, bare tip). The power delivered down each fibre was 100 mW, checked with a power meter prior to use. 18 gauge needles were positioned trans-orally or percutaneously into the tumours at approximately 1.5 cm intervals. Ultrasound, CT, or MRI guidance was used for needle insertion into deep-seated tumours, particularly for those thought to lie close to vital structures such as the carotid artery, cervical vertebrae or the skull. The fibres were passed through the needles using a flagging system to ensure that the fibre tip was exposed to the tissues and not still inside the needle. Up to four fibres were positioned at a time and a pullback technique was used with 1cm steps to treat thicker tumours. The energy applied at each treatment site was 20 joules. After administration of mTHPC, patients followed a regime of controlled re-exposure to light over a period of 2-3 weeks.

Assessment and Follow-up

4 weeks after PDT, the results were assessed as: complete response (CR): no evidence of disease; partial response (PR): 50% decrease of the tumour volume; stable disease (SD): no change in tumour size enough to describe as PR or PD; progressive disease (PD): an increase of at least 25% in the size of measurable lesions or the appearance of any new lesions. Tumour volume was estimated by physical and radiographic measurements before and after PDT. Most treatments were carried out with palliative intent and the results assessed objectively and subjectively.

Results

Between July 1997 and December 2002, 45 patients were treated with salvage IPDT. Six underwent IPDT without complications, but were lost to follow-up before their one-month assessment, so were excluded from the subsequent analyses. Details of the remaining 39 patients with recurrent (36) or persistent (3) cancers and their management prior to PDT are summarized in table 1. Tumour details are summarized in table 2.

Excluding the six patients lost to early follow-up, 61 treatments were performed on 39 patients. The laser fibres were inserted trans-orally, percutaneously, or both in 34 (56%), 22 (36%), and 5 (8%) treatments, respectively. Twenty-four patients (62%) received a single treatment; 10 patients (26%) received two treatments, four patients (10%) received three and one patient received five treatments. 21% (8/39) of the treated tumours were close to major structures deep in the neck (e.g. carotid artery), another 21% (8/39) had invaded up under the base of skull, whilst 15% (6/39) had compressed the trachea. The one month response could be assessed after 56 of these 61 treatments. CR was achieved in 8 treatments (8 patients, 14%); PR was achieved in 42 treatments (75%), one of which became a CR with additional treatment, as described below, SD was noted in 4 (7%) whilst PD was encountered in 2 treatments (4%). The overall response rate (CR + PR) was 50/61 (82%).

Although the patients in this study had failed conventional therapy, seven were treated with curative intent because of the relatively early stage of recurrent disease. Four had a CR after IPDT. Two others only had PR and subsequently died of their disease 9 and 17 months later. A young girl with a 5cm alveolar soft part sarcoma of the hard palate had a limited tumour resection and full courses of ifosfamide, vincristine and actinomycin-D before IPDT, but still had progressive disease. After two treatments with IPDT, only microscopic tumour was detectable. After radiotherapy and a further local resection she became disease-free and is now alive and well 5 years later (Fig 1). Four further patients, who were treated initially with palliative intent, had a CR. Of the nine patients who achieved disease free status, five are still alive and free of disease 10-60 months after PDT (Table 3).

In addition to the four patients who had a CR, a further 28 patients with more advanced disease were treated with palliative intent. Nineteen of these were fed through a gastrostomy and five also had a

tracheostomy. One patient had a tracheostomy without a gastrostomy. Eight had bulky tumours, but were able to maintain oral nutrition. In all but five, the main clinical problem was the tumour bulk (median 48cm^3, range 12-228cm^3). Some had more than one dominant symptom. It was not possible to improve swallowing or close the tracheostomy in any of these individuals. Nevertheless, PDT reduced the tumour bulk with subjective benefit for the patients in 17 of 23 cases. Bleeding was stopped in 3 of 3, dyspnoea was relived in 1 of 2 and brachial plexus compression was relived in 1 of 1, but pain was only helped in 2 of 5 cases. Thus clinical benefit was achieved for 24 of the 33 dominant symptoms. MR images of one patient before and after PDT to reduce bleeding are shown in Fig 2. Of the 21 patients in this group who achieved worthwhile palliation from PDT, eight survived for more than a year (including two who are still alive, 24 and 31 months after PDT). All seven patients who did not respond to PDT were dead within 2 months. For the whole group of 39 patients, the median survival (Kaplan-Meier) was 14 months (Fig 3). For the 32 patients responding to PDT, the figure was 16 months. For the seven who did not respond, it was only 1 month. Patients with squamous carcinomas had a slightly shorter survival compared with other pathologies (not significant).

Eight patients had treatments in close proximity to the facial nerve, 15 were close to the hypoglossal nerve and two were close to the brachial plexus. The only neurological deficits prior to PDT were in two hypoglossal nerves and one brachial plexus. After PDT, there was no further loss of function in any of these nerves and in the patient with a brachial plexus deficit, voluntary arm movement improved after PDT.

Complications

The expected post-treatment pain and swelling subsided in 2-4 weeks. There was no treatment related airway obstruction. The only major treatment related complication was a carotid blow out 2 weeks after PDT in a 33 year-old lady with recurrent neck disease. On an MR scan taken 1 month prior to IPDT, the tumour was judged to be close to, but not involving the carotid artery. Post-mortem examination showed malignant cells along the intima of the carotid artery implying tumour invasion. Skin photosensitivity was noted in one patient who failed to comply with the recommended regime for light exposure.

Discussion

Despite the advances in oncology during the last few decades, most patients with recurrent head and neck cancer still succumb to their disease in a relatively short period of time. The patients in this study were all referred for "last hope" salvage treatment, having been considered unsuitable for further treatment with surgery, radiotherapy or chemotherapy. Nevertheless, five patients (13%) are alive and apparently free of disease 10-60 months later, and the median survival time for the 32 patients (82%) who responded to PDT was 16 months.

Damage to cranial nerves and major blood vessels during salvage surgery or radiotherapy is difficult to prevent and greatly reduces the patients' quality of life. In the present study, the treated tumour encased or was in close proximity to important nerves in 24 patients, but no loss of function was detected and in one case (brachial plexus compression), nerve function improved after PDT. Thus anecdotally, nerves seem to tolerate PDT well. There is also good experimental evidence that the risk of thrombosis or rupture of normal arteries after PDT is minimal, due to preservation of elastin and collagen fibres.[9] Better imaging should reduce the risk of treating arteries invaded by tumour. The carotid blow-out was our only serious complication. The willingness of patients to undergo repeat treatments showed that the technique was well tolerated.

Our results compare favourably with other therapeutic options. Salvage surgery is rarely curative and carries a 20-40% risk of serious complications.[10,11] Similarly, many different salvage radiotherapy regimens have been used, including external beam, interstitial "high-dose-rate" or "low-dose-rate" brachytherapy.[3,12,13] Although 20-30% of patients may survive for 2 years, moderate to severe complications (including carotid blow-out) have been reported in 30%-40% of cases. Chemotherapy for these recurrent cancers has a response rate of no more than 10%-30% with a median survival of about 6 months.[14] Newer drugs have not improved the response rates significantly from those seen with traditional cisplatin-based chemotherapy.[15]

Two of the 3 sarcomas treated in this study responded remarkably well. The young girl with a sarcoma of the palate is free of disease at 5 years and the older patient with a skull base osteosarcoma had good relief from his headache. PDT may be able to play an important role in the management of these rare

tumours, especially those occurring in surgically inaccessible sites, as the response to chemotherapy and radiotherapy is not always good.[16]

Conclusions

Recurrent head and neck cancers are difficult to treat because of the complex regional anatomy and close proximity to vital structures. This study shows that IPDT can be an effective salvage measure for these unfortunate patients. It is minimally invasive, effective for carcinomas and sarcomas and can be used in patients who are unfit for further radiotherapy or surgery. It is a therapeutic option that is likely to become a useful addition to the armamentarium of the integrated head and neck oncology team for late stage disease.

References

1. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer Incidence and Mortality in the European Union: Cancer Registry Data and Estimates of National Incidence for 1990. European Journal of Cancer 1997; 33:1075-1107.

2. Watson JC, Ridge JA. Surgical management of local and regional recurrent head and neck squamous cell carcinoma. Curr Opin Oncol 1998; 10:207-212.

3. De Crevoisier R, Bourhis J, Domenge C, Wibault P, Koscielny S, Lusinchi A, Mamelle G, Janot F, Julieron M, Leridant AM, Marandas P, Armand JP, Schwaab G, Luboinski B, Eschwege F. Full-dose reirradiation for unresectable head and neck carcinoma: experience at the Gustave-Roussy Institute in a series of 169 patients. J Clin Oncol 1998; 16:3556-3562.

4. Stewart FA. Re-treatment after full-course radiotherapy: is it a viable option? Acta Oncol 1999; 38:855-862.

5. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, Moan J, Peng Q. Photodynamic therapy. JNCI Cancer Spectrum 1998; 90:889-905.

6. Hopper C. Photodynamic therapy: a clinical reality in the treatment of cancer. Lancet Oncol 2000; 1:212-219.

7. Fan K, Hopper C, Speight PM, Buonaccorsi GA, Bown SG. Phoyodynamic therapy using mTHPC for malignant disease in the oral cavity. Int J. cancer 1997; 73:25-32

8. Bown SG, Rogowska AZ, Whitelaw DE, Lees WR, Lovat LB, Ripley P, Jones L, Wyld P, Gillams A, Hatfield AWR. Photodynamic therapy for cancer of the pancreas. Gut 2002; 50:549-557.

9. Grant WE, Buonaccorsi G, Speight PM, MacRobert AJ, Hopper C, Bown SG. The effect of photodynamic therapy on the mechanical integrity of normal rabbit carotid arteries. Laryngoscope 1995; 105:867-871.

10. Rate WR, Garrett P, Hamaker R, Singer M, Pugh N, Ross D, Haerr R, Charles G. Intraoperative radiation therapy for recurrent head and neck cancer. Cancer 1991; 67:2738-2740.

11. Marcial VA, Hanley JA, Ydrach A, Vallecillo LA. Tolerance of surgery after radical radiotherapy of carcinoma of the oropharynx. Cancer 1980; 46:1910-1912.

12. Puthawala A, Nisar S, Gamie S, Chen YJ, Londre A, Nixon V. Interstitial low-dose-rate brachytherapy as a salvage treatment for recurrent head-and-neck cancers: long-term results. Int J Radiat Oncol Biol Phys 2001; 51:354-362.

13. Glatzel M, Buntzel J, Schroder D, Kuttner K, Frohlich D. High-dose-rate brachytherapy in the treatment of recurrent and residual head and neck cancer. Laryngoscope 2002; 112:1366-1371.

14. Clavel M, Vermorken JB, Cognetti F, Cappelaere P, de M, Schornagel JH, Tueni EA, Verweij J, Wildiers J, Clerico M. Randomized comparison of cisplatin, methotrexate, bleomycin and

vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1994; 5:521-526.

15. Forastiere AA, Shank D, Neuberg D, Taylor SG, DeConti RC, Adams G. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer 1998; 82:2270-2274.

16. Casanova M, Ferrari A, Bisogno G, Cecchetto G, Basso E, De B, Indolfi P, Fossati B, Carli M. Alveolar soft part sarcoma in children and adolescents: A report from the Soft-Tissue Sarcoma Italian Cooperative Group. Ann Oncol 2000; 11:1445-1449.

Table I. Patient details. Many primary and some salvage treatments prior to PDT included more than one therapeutic modality.

Median age	58 years (range 8-84)
Sex	
Male	25 (64 %)
Female	14 (36 %)
Primary treatment	
Surgery	15 (38 %)
Radiation	35 (90 %)
External only	25
External & brachytherapy	3
Concurrent chemotherapy	7
Salvage treatment after recurrence	16 (41 %)
Surgery	12
Brachytherapy	3
Palliative chemotherapy	3

Table 2. Tumour details.

Tumour location	No. of patients	Tumour location	No. of patients
Anterior tongue	6	Tonsillar region	5
Buccal mucosa	2	Oropharyngeal wall	2
Floor of mouth	4	Maxillary sinus	2
Alveolar ridge	3	Nasal cavity	3
Hard palate	3	Nasopharynx	1
Tongue base	1	Parotid	2
Neck	4	Thyroid	1

27 were squamous cell carcinomas and 3 were adenocystic carcinomas. There was one each of: basal cell carcinoma (parotid gland), olfactory neuroblastoma, follicular cell carcinoma, haemangiopericytoma, branchiogenic carcinoma, primitive neuroectodermal tumour, malignant fibrous histiocytoma, osteosarcoma and alveolar soft part sarcoma. Tumour staging at the time of PDT was: rT2:3, rT3:3, rT4:31, rN2:1, rN3:1. The median estimated tumour volume was 38 cm^3 (range 8-224 cm^3).

Table 3. Summary of complete responders and disease-free patients

Case no	Age at IPDT	Sex	Treatment site	Pathology	Stage Original/recurrent	Previous treatment	Time from initial tx to IPDT (month)	Tumour volume (cm^3) prior to PDT	Disease-free time (month)	Follow-up time (month)	Outcome
1	52	M	Neck	SCC	N3/N2	R, S	18	12	14	17	LR
2	57	F	HP	SCC	T2/T4	R	30	32	NER	22	UD
3	60	M	TB	SCC	T4/T4	CR, B	46	80	12	17	LR
4	82	F	AR	SCC	T4/T2	S, S	5	8	NER	13	AW
5	21	F	Tongue	SCC	T1/T3	S, S	24	12	26	32	LR
6	52	M	FOM	SCC	T4/T3	S, R	5	10	NER	10	AW
7	59	M	Tongue	SCC	T4/T4	CR	8	60	NER	28	AW
8	42	F	Parotid	ACC	T4/T4	S, R	46	32	NER	15	AW
9*	8	F	HP	ASPS	T2B/T2B	C, S	3	20	NER	60	AW

ACC: adenoid cystic carcinoma, AR: alveolar ridge, ASPS: alveolar soft part sarcoma, AW: alive and well, B: brachytherapy, C: chemotherapy, CR: chemoradiation, FOM: floor of mouth, HP: hard palate, LR: died of local recurrence of disease, NER: no evidence of recurrence at the last follow-up, R: radiotherapy, S: surgery, SCC: squamous cell carcinoma, TB: tongue base, tx: treatment, UD died of unrelated disease,

*Two IPDT treatments were performed to debulk the tumour followed by radiotherapy and local excision for persistent microscopic disease. Since then, she has been free of disease.

Figure Legends

Fig 1. Alveolar soft part sarcoma in an 8 year-old girl. A: Palate viewed immediately before the first IPDT. A retractor (dark arrows) was applied to the upper lip (UL) exposing the bulky tumour that occupied the whole hard palate with extension to the soft palate and the right palatine tonsil. Black shields (B) were used to protect the tongue (T) and normal oral mucosa. White arrows indicate the endotracheal tube. B: Palate viewed 4 weeks after her second IPDT. A mirror was put on her tongue and chin (C) to show the post-treatment condition. Dark arrows indicate the lateral edge of the mirror. There was no visible tumour, although an oro-nasal fistula (white arrows) had developed. A biopsy at this time showed persistent tumour microscopically, but after a local excision and radiotherapy, she became disease free and has remained well for 5 years.

Fig 2. Magnetic resonance images of a maxillary cancer in a 76 year-old man with recurrent episodes of massive nasal bleeding requiring transfusion. A: T2-weighted MRI before IPDT, showing a tumour in the right maxillary antrum and peri-orbital invasion. B, T1-weighted MRI during treatment showing the position of the MR compatible needles prior to insertion of Laser fibers. The needles appear as small, dark (low signal intensity) areas within the tumour mass. C, T2-weighted MRI 6 weeks after treatment demonstrating a dramatic reduction of tumour bulk. Nasal bleeding stopped after IPDT and the patient lived for a further 19 months.

Fig 3. Overall survival (Kaplan-Meier curves).

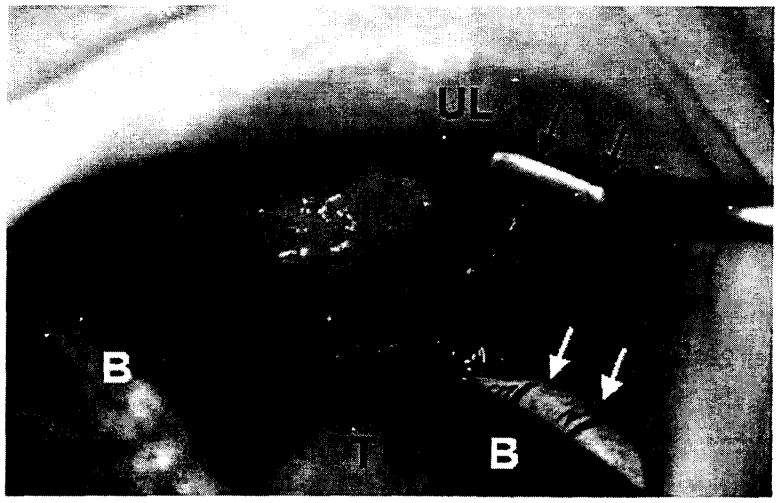

Fig 1A.

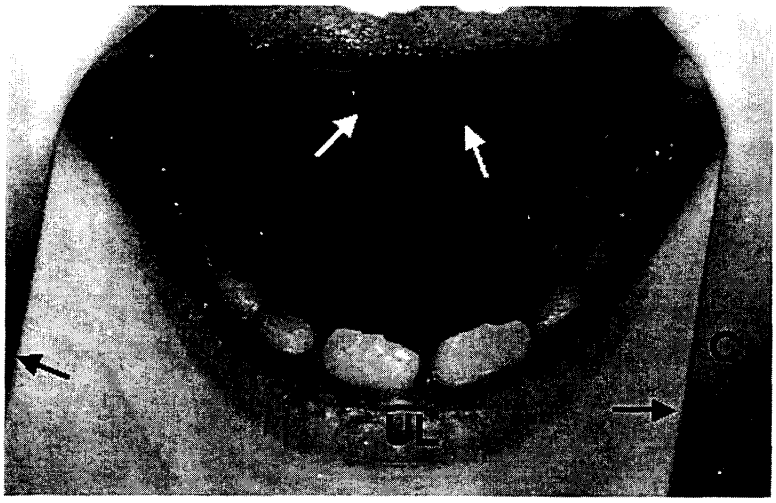

Fig 1B.

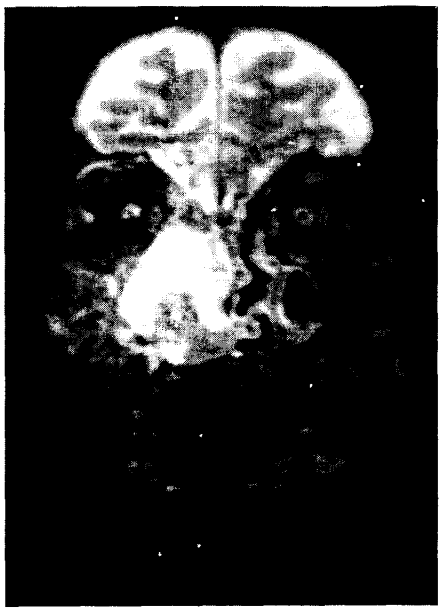

Fig 2A.

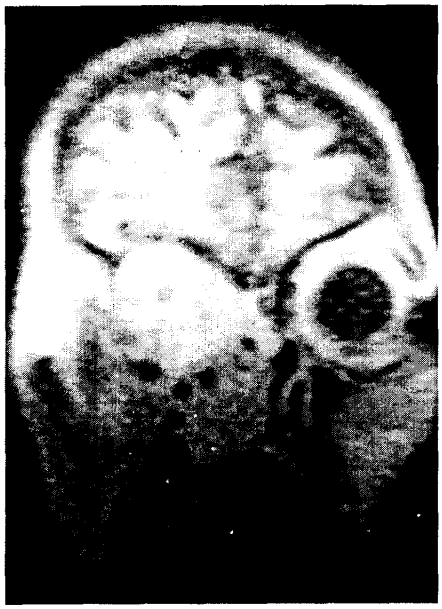

Fig 2B.

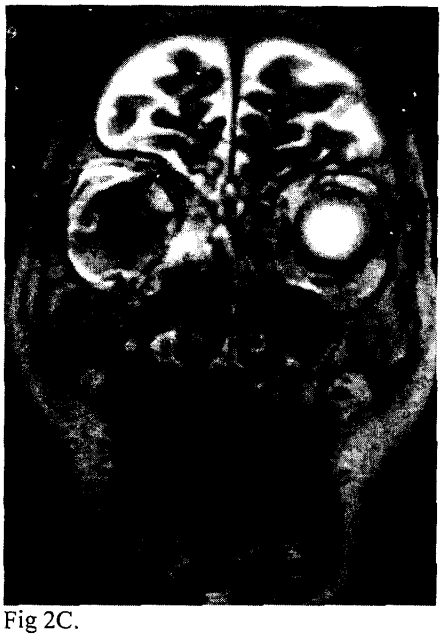

Fig 2C.

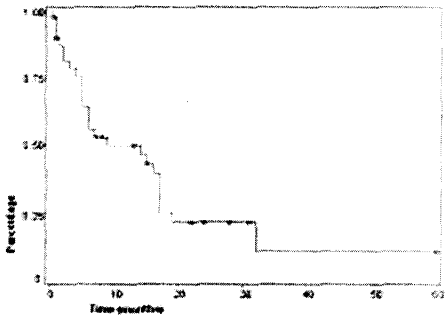

Fig 3.