National Institute for Health and Clinical Excellence

538 – Photodynamic therapy for brain tumours

Consultation Comments table

IPAC date: 15th January 2009

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 NHS Professional University Academic	1	This is quite unclear. Safety of what? - 3 drugs have been used in detection and treatment of brain tumours, ALA perfectly safe and useful as a surgical adjunct, Photofrin which has been used on several thousand patients safely (there may be issues with very high light doses as in Krishnamurthy paper) Foscan, where my personal series is about 1,000 treatments (mainly head and neck where the treatment is approved). A very clear difference should be drawn between the safety of the therapy and the safety of the therapy when used in the brain specifically	Thank you for your comment. Section 1.1 relates specifically to the evidence available for this indication, but does not distinguish between the type of photo-activating drug used in the brain.
2	Consultee 2 NHS professional	1	I agree entirely with this remark	Thank you for your comment.
3	Consultee 1 NHS Professional University Academic	2.1	No mention of PDT guided resection	Thank you for your comment. This falls outside the scope of the guidance and section 2.2 of the guidance will be changed to ensure this is clear to the reader.

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4	Consultee 2 NHS professional	2.1.1	2.1.1 - comment regarding survival of only a few months is too pessimistic - median survival for GBM (worst prognosis tumour) is 14 months in recent trials and over 25% of patients are surviving over 2 years.	Thank you for your comment. Section 2.1.1 of the guidance will be changed.
5	Consultee 3 NHS Professional Specialist Adviser	2.1.1	2.1.1 meningiomas are graded grade 1 to 3 there is no grade 4 there is no mention of pituitary adenoma	Thank you for your comment. Section 2.1.1 of the guidance will be changed.
6	Consultee 4 NHS Professional Society of British Neurological Surgeons	2.1.1	I am writing on behalf of the Society of British Neurological Surgeons (SBNS) to comment on the above consultation document. Please accept the following comments on behalf of the SBNS. 1. Meningiomas are graded 1 to 3 and not I to IV (Paragraph 1) 2. Pituitary tumours to be considered for inclusion for the therapy.	Thank you for your comment. Section 2.1.1 of the guidance will be changed. Pituitary tumors fall outside the scope of the guidance.
7	Consultee 2 NHS professional	2.1.2	2.1.2 - Â could be much better written for clarity. brain tumours present in 3 principle ways: symptoms of raised intracranial pressure, progressive neurological deficits, or seizures.	Thank you for your comment. The Committee considered this section explained the symptoms appropriately. The guidance will not be changed.
8	Consultee 2 NHS professional	2.1.3	2.1.3 - not clear nor accurate. patients are treated with surgical resection with the aim of improving symptoms and improving prognosis (survival). for the majority of patients surgery is not curative with the exception of rare WHO grade I gliomas and meningiomas	Thank you for your comment. Section 2.1.3 states that in most patients curative resection is not possible. The guidance will not be changed.
9	Consultee 3 NHS Professional Specialist Adviser	2.1.3	2.1.3 grade 1 and 2 meningiomas are routinely completely excised. Â recurrence risks are low - approx 10-20% at five years	Thank you for your comment. Section 2.1.3 states that in most patients curative resection is not possible. The guidance will not be changed.

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10	Consultee 1 NHS Professional University Academic	2.2	I would not call it a low power laser - there is no heat involved "a laser light source" is more accurate	Thank you for your comment. Section 2.2.1 of the guidance will be changed.
11	Consultee 2 NHS professional	2.2	avoidance of light for several weeks has a major adverse effect on quality of life and this needs to be accounted for in studies. if survival advantage is only several weeks and that survival if poor quality then it is of no real benefit.	Thank you for your comment. This section of the guidance is intended to be a summary of the procedure. The short survival advantage was recognised when the recommendations were agreed and the guidance will not be changed.
12	Consultee 1 NHS Professional University Academic	2.3	I feel it is important to specify exactly which drugs are involved in each study - most of these studies are with porphyrin drugs, but some more recent studies are using Foscan - which I do not think was used as a search tool. On a quick pubmed check, I do not think anything important was missed however	Thank you for your comment. This detail can be found in the overview for this topic. Foscan was not used as a search term however the other terms used are likely to have identified all relevant clinical studies. Cross referencing from included studies was also undertaken. The guidance will not be changed.
13	Consultee 2 NHS professional	2.3.1	2.3.1 - i am not sure how this remarkably small RCT study was powered. the treatment arm had a median survival the same as the control arms in other major RCTS for high-grade glioma (cf carmustine wafers and temozolomide NICE appraisals) - approx 12 months! the control arm in this study did extermely poorly compared with these other RCTS - only 6 months survival. no sensible conclusions about efficacy can be drawn from the data presented here. further better conducted RCTS are clearly required	Thank you for your comment. The Committee were aware of the limitations of the available evidence and the recommendation in 1.1 states that this procedure should only be used in the context of randomised controlled trials.

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14	Consultee 1 NHS Professional University Academic	2.4	I dont think hypersensitivity has been seen. Basic safety databases for all PDT drugs are available and include controlled reexposure to light (so that skin sensitivity is avoided), risks of nerve damage and risks of damage to blood vessels.As for the "theoretical aes" this suggests the authors have little experience with the therapy. Was there any input from the broader PDT community about overall safety of the therapy? (BMLA/EPPM/IPA) Also, I make 1/112 less than 1%(2.4.3)	Thank you for your comments. Section 2.4.4 of the guidance represents the opinion of the Specialist Advisers. Section 2.4.3 of the guidance will be changed.
15	Consultee 2 NHS professional	2.4	Much higher numbers from RCTS needed to properly assess the risks of this treatment that include death. also should consider length of stay as routine length of stay for routine resection of GBM (+/- insertion of carmustine wafers) should now be 1-2 days only, not 7 in this RCT. why is this?	Thank you for your comment. The recommendation in 1.1 states that this procedure should only be used in the context of randomised controlled trials. The overview provides more details about individual studies.
16	Consultee 5 NHS Professional Specialist Adviser	General	Could I say how pleased I am with the NICE provisional recommendations? I think they distil the problem down to the essential one: lack of randomised control trial evidence. As the BSNR representative could I suggest that photodynamic therapy requires same type of inclusive study that assessed cerebral aneurysm coiling (ISAT) undertaken with the BSNR and BSNS by the Oxford group so successfully. I think there needs to be inclusion of more centres using photodynamic therapy for the technique to be assessed with sufficient clinical equipoise to be used to inform NICE and other policy makers. I believe the BSNR would be very willing to contribute to this process as imaging would be a crucial surrogate end point in addition to patient survival and post surgical outcomes.	Thank you for your comment. The recommendation in 1.1 states that this procedure should only be used in the context of randomised controlled trials. We would like to express our appreciation at your offer of a collaborative group and encourage development of further trials.

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17	Consultee 6 NHS Professional Specialist Adviser	General	The author had done a great job getting this together in such a short time. However, I have few comments on the matter: 1- PDT can not be separated from PD and fluorescence guided resection and the topic should be Fluorescence guided surgery and PDT in brain tumours.	Thank you for your comments. 1. The scope of the guidance excluded Fluorescence guided surgery alone, but did include PDT alone, or PDT following fluoresce guided surgery; the vast majority of the data was in this last group. The guidance will not be changed.
18	Consultee 6 NHS Professional Specialist Adviser	General	I am not sure what if any of the Association of British Neurologists, British Society of Neuroradiologists and British Association of Head and Neck Oncologists have any stakes in the procedure, as I doubt if any of their members had used it seen it in use or even knew about the technology. I would have thought that you should have sought expert opinions from The British Medical Laser Association with Prof Harry Moseley as President http://www.bmla.co.uk/, The British PDT Interest Group with Prof Keyvan Miggisshi as chairman and Editor in Chief of Photodiagnosis and Photodynamic Therapy http://www.elsevier.com/wps/find/journaldescription.cws_home/701993/description#description and Eurpean Platform for Photodynamic Medicine (EPPM) with Prof Herwig Kostron as vice president in Innsbrock, Austria and finally the International Photodynamic Association (IPA), http://www.pms.ac.uk/ipa/index.php, would be a better choice as they would know what are they talking about.	Thank you for your suggestions. These groups were approached to see if they would wish to offer specialist advice to NICE on this procedure. The societies / associations that contributed specialist advice are listed in the overview. However, we will approach the British Medical Laser Association and the British PDT Interest Group in future for specialist advice on relevant procedures.

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19	Consultee 6 NHS Professional Specialist Adviser	General	5-aminolevulenic acid (ALA) had not been included in the review. ALA is given orally and photosensitivity only lasts for 24 hours and used for both PDT and PD. with a multicentre randomised study from Germany published in 2006 in lancet Oncology. I hope that you would consider widening the review to be inclusive of all agents including ALA and fluorescence resection as well as widening the stake holders expert panel to include reps from other stake holders associations mentioned above to benefit our patients who are desperate for treatment that can improve their chances of fighting this deadly cancer without the risk of radiation or chemo.	The consultee may wish to notify this intervention to the IP Programme. Our current guidance will not be changed.
20	Consultee 7 NHS Professional	General	I read with interest the Interventional procedure overview of photodynamic therapy for brain tumours. While welcoming this brief document, i would like to add a few comments of my own.	Thank you for your comments.
21	Consultee 7 NHS Professional	General	PDT does not damage underlying nerves, tendon, collagen or bone and scarring is minimal. It has the advantage that it can be repeated; we have experience of treating the same site up to four times without any drawbacks. This has also been reported in the literature, when there has been incomplete removal or recurrence, or for palliation. There is apparently no cumulative toxicity from multiple treatments.	The guidance and the overview acknowledge that ‘occasionally, repeated PDT sessions are performed’.

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22	Consultee 7 NHS Professional	General	We have also been exploiting the tumour detecting possibilities of photodiagnosis. In this case, a laser emitting a shorter wavelength is used and this induces fluorescence in the areas of photosensitizer uptake. We are finding this particularly useful in identifying islands of cancer cells left following surgical removal of glioblastoma.	This falls outside the scope of the guidance.
23	Consultee 7 NHS Professional	General	Fluorescence-guided resection is a technique that is being developed and shows great promise. We are using ALA, a drug that has no systemic photosensitisation problem.	The scope of the guidance excluded Fluorescence guided surgery alone, but did include PDT alone, or PDT following fluoresce guided surgery; the vast majority of the data was in this last group.
24	Consultee 7 NHS Professional	General	PDT does not preclude use of other treatments and can be combined with other therapies, such as radiotherapy, chemotherapy, stenting and surgery.	Concomitant treatments used in the studies included are described in the overview, in the first column of table 2.
25	Consultee 7 NHS Professional	General	Sunburn is a very mild side-effect. It can be prevented by educating the patient, carer,and hospital staff. It can be easily managed if it occurs.	Thank you for your comment.
26	Consultee 7 NHS Professional	General	While recognising the value of the multi-centre randomised clinical control (RCT) it should be recognised that this is very expensive and cannot be undertaken without a significant sponsor. Since there is no major pharmaceutical company involved in PDT, it is very difficult to conduct an RCT. It is important that a potentially useful therapy is not lost because there is no major pharmaceutical company to promote this modality.	The Committee recognise the practical problems regarding the development of an RCT and recommend such only in instances where this research would make a significant contribution to the evidence base to inform future guidance

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27	Consultee 7 NHS Professional	General	We have always been willing to provide specialist training from our centre and recognise the responsibility of those who are currently deliver PDT to share their knowledge in the use of this technology, including light delivery systems	Thank you for your comment.