

The Future of Photodynamic Therapy 17th July 2014

Executive summary

This meeting was planned to bring together those interested in the potential of PDT as a therapy for cancer and representatives of CRUK and the NCRI Clinical Study Groups (CSG's) to review the evidence of efficacy of PDT. The aim was to identify the most promising indications and the trials that should be undertaken to establish which of these might find a place in routine clinical practice.

Overviews of the current use of PDT were given for a broad range of specialties, followed by breakout groups for more detailed discussion of potential trial designs in specific cancer indications, and a final plenary session to bring the conclusions together.

It was agreed that there is a need for PDT researchers to engage and win the support of the broader clinical scientific community. Clinical trial concepts should be discussed at an early stage with the relevant CSG's so that the potential role of PDT can be considered in the context of other treatment approaches. The aim must be to develop clinical trials which are considered by the whole cancer research community to be worthwhile, scientifically sound and feasible as part of the overall clinical research portfolio.

New Trial Concepts

Several outline concepts were put forward from the break-out groups for further consideration and discussed in the closing session. A proposer was identified for each, to work up the concept into a short document outlining the rationale for the study, study hypothesis, patient population to be treated and clinical endpoint(s). Proposers are also asked to discuss their concept with an NIHR registered Clinical Trials Unit or Research Design Service to get input on methodology and statistics.

The concept should then be submitted for discussion to the relevant CSG (or CSG Subgroup) Chair via the NCRI CSG Secretariat. Practices of the CSG's vary, but some are likely to invite the proposer to attend a CSG or Subgroup meeting to present their concept.

Skin Cancers

- **RCT1: Prevention of SCC in high risk organ transplant recipient patients.** Comparing treatment of large field v. no field treatment.
- **RCT2: BCC and the treatment of multiple lesions. Four arm trial design - PDT v. Imiquimod v. Excision v. Curettage.** Trial Outcomes – Efficacy, Health economics and PROMs
- **Phase I/II Study: intraepithelial neoplasia basket study.** To test efficacy of second generation photosensitizing agents in intraepithelial neoplasia of the genitalia or anus (VIN; CIN PeIN; AIN). To be discussed with Gynae, Bladder and Colorectal CSG's. Consider collaboration with ongoing trials in Germany

Head & Neck

- **Questionnaire.** To capture the perception of PDT within the Head & Neck Clinical community and willingness to participate in multi-centre clinical trials.
- **RCT1: Non-inferiority study of surgery vs. PDT for early oral cancer.**
- **RCT2: RCT for end stage disease - Palliative chemotherapy v. PDT + chemotherapy or PDT v. palliative chemotherapy or crossover study.**

Oesophagus

- **Phase I/II study of PDT for localised recurrence after first line treatment,** followed by a non-inferiority study of PDT v standard treatment (stent/RT/chemo).

Bladder

- **Phase I/II Study: intraepithelial neoplasia basket study.** Includes PeIN (penile). See entry in Skin section. Penile Cancer is a subgroup of the Bladder CSG.

Colorectal

- **RCT: TEM (Transanal Endoscopic Microsurgery) +/- adjuvant PDT.** For small rectal cancers; aiming to reduce incidence of local recurrence
- **Phase I/II Study: intraepithelial neoplasia basket study.** See entry in Skin section. Anorectal Cancer is a subgroup of the colorectal cancer CSG.

Brain Cancer

- **(R)CT of stereotactic, interstitial PDT of glioblastoma v. conventional surgery** if trend of benefit in current uncontrolled stereotactic trial in Munich continues. Potential collaboration with Munich team.

Gynaecological Cancer

- **Phase I/II Study: intraepithelial neoplasia basket study.** Includes vulval - see skin cancer section, above

Existing Trials in progress or setup

In addition to the new concepts listed above, the breakout groups noted a number of clinical trials that are already in development or underway. Some of these will be too far advanced to ask CSG's for input in their design; however, Chief Investigators should make contact with the relevant CSG Chair (or CSG Subgroup Chair) to make them aware of the study. Wherever possible, eligible studies should be submitted for inclusion in the NIHR Clinical Research Network Portfolio.

The following trials in development or ongoing were identified:

Head & Neck

- **Phase II study of PCI for advanced head & neck cancer.** A commercially sponsored study, already on the NIHR commercial portfolio, funded by PCI Biotech.

Lung

- **RCT of PDT v active surveillance for pre-invasive disease in the major airways.** This study had been put forward for NIHR funding, which was not awarded.

Bladder

- **RCT: comparing the clinical and cost effectiveness of white light v Hexvix fluorescence for guidance of TUR for non-muscle invasive bladder carcinomas.** This study is NIHR funded and in setup.

Colorectal

- **Phase I/II study: Detection of metastatic nodes at laparoscopy with ALA-fluorescence.** This study is already funded by the MRC.

Prostate

- **RCT: Phase III study of PDT v active surveillance for low grade cancer localized to the prostate.** 400 patients have been recruited. This study is funded by Steba Biotech and is close to completion.

Pancreas/Biliary tract

- **Phase II study of PDT for locally advanced pancreatic cancer** with light delivery under direct endoscopic ultrasound guidance.
- **Phase I/II study of PDT with liposomal chemotherapy for locally advanced pancreatic cancer.**
- **Phase I/II study of PCI for biliary cancer.** This study is funded by PCI Biotech

Breast

- **Phase I/II Single fibre PDT for small tumours (1-2cm); Phase I/II Multifibre PDT for larger tumours** with RT to the margins. Partly funded by Killing Cancer and the Royal Free Charity

Introduction. Peter Johnson (Chief Clinician, CRUK)

PDT is an area of considerable interest, but also of considerable controversy. There are two likely reasons – a relatively poor evidence base or contested evidence and the presence of significant vested interests.

CRUK has been involved in aspects of PDT for many years. It funded the Patterson lamp for skin PDT in Manchester as well as some clinical trials.

This meeting aimed to review the evidence, to identify where the current research gaps are and to determine where research is most likely to be productive.

Review of PDT across oncology. Chair: Steve Bown

Current status of PDT. Laurence Lovat

The key strengths of PDT are the nature of the biological effect (different from chemotherapy, radiotherapy, surgery and heat treatment), the lack of cumulative toxicity, the lack of effect on connective tissues such as collagen, some selectivity of photosensitizer uptake in cancers (although this is often over emphasized) and the focal nature of treatment, based on the geometry of light delivery.

The major problems are a lack of high quality data supporting the use of PDT with most studies small and uncontrolled and side effects from first generation photosensitisers (mainly prolonged skin photosensitivity) resulting in a lack of interest from the major pharmaceutical companies.

Fresh opportunities exist with the advent of photosensitisers with a much shorter duration of skin sensitivity, some of which stay in the vasculature, so clear within a few hours. Coupling antibodies to photosensitisers markedly improves tumour selectivity. Experimental studies using repeated treatments with photosensitizer coupled to a HER-2 antibody fragment have shown much higher tumour clearance rates than using photosensitizer without antibody coupling.

Patient Focus. George Smith

Professor George Smith FRS provided a patient perspective, presenting his and his late wife Josie's views on PDT after her treatment for vulval extra-mammary Paget's disease. The recent Cochrane report on Paget's disease stressed that patients strongly preferred conservative treatments. He emphasized three aspects of PDT based on their experience:

1. Acceptability. PDT minimises the risks of surgical complications and infection, is undertaken as an outpatient, does not have the collateral effects of chemotherapy and radiotherapy and is repeatable.
2. Best Practice: a great variability in the quality of treatment delivery, which is sometimes poor in the NHS.
3. Combined Treatments. Some advantages. In his wife's case, the combination of PDT with imiquimod was more effective than either alone.

He identified a range of weaknesses in the way PDT was delivered in the various centres that had treated his wife and suggested that training programmes would lead to better and more consistent clinical practice.

Introduction to specific tumour types

Skin Cancer: John Lear

Skin cancers and pre-cancers are very common. Almost everyone in Australia over 50 has actinic keratosis (AK). Even in northern England, it can affect 20% of over 60's.

Although AK, Bowen's disease and basal cell carcinoma (BCC – about 300,000 patients currently in UK) are considered one of the most established areas for PDT, concerns still exist regarding the lack of high quality evidence, in particular the role of PDT for patients with multiple BCC lesions.

More randomised studies, particularly with PROM's (patient reported outcome measures) are needed, as well as more work to establish which BCC's are most suited to PDT. Cosmesis and cost effectiveness need assessment, compared with surgery. A recent paper in Lancet Oncology compared PDT with imiquimod, but with only a one year follow up.

Possible future trials would include skin cancer prevention over large areas in organ transplant recipients and Gorlin's syndrome, in a randomised study comparing Imiquimod and PDT or the combination of both and the efficacy and feasibility of daylight activation of photosensitisers.

Intraepithelial neoplasia at mucocutaneous junctions (vulva, anus, penis) has been shown to be promising for PDT and this presents possibilities for collaboration between dermatology, gynaecology, colorectal surgery and urology

Head & Neck Cancer: Colin Hopper

There is a substantial body of published work on PDT for head & neck cancer. Key attractions are repeatability, good healing, minimal neurotoxicity and possibility of use when other treatments have failed or are considered inappropriate.

There are no RCT's comparing PDT with conventional therapy.

For many early oral cancers, simple excision is feasible. If this is not straightforward, the relative rarity of the condition and the enormous variability between individuals makes it difficult to identify suitable groups for randomisation between PDT and alternatives such as surgery and radiotherapy, but such a study needs to be done.

For advanced oral disease (a licensed indication when all other standard treatments have failed), the only realistic comparator is chemotherapy and patients are likely to be reluctant to be randomised between these 2 choices. This might be addressed in a cross over study, using the second treatment option if the first has not been effective in a specified period, perhaps 6-8 weeks. There is little need for further phase 1 dose ranging studies.

Recent developments include work on PCI (photochemical internalization) using the photosensitizer amphinex to release bleomycin from lysosomes. A phase I study has shown safety and possible improved selectivity compared with PDT.

Thus future trials could include:

1. RCT of PDT v surgery for early oral cancer
2. Mapping neoplastic areas (by photosensitizer fluorescence) and treatment at the same session.
3. RCT's for nasopharyngeal cancers failing radiotherapy (PDT compared with chemotherapy)
4. RCT's for localised laryngeal disease (PDT v surgery for RT failures).
5. PCI (photochemical internalization) is an important new development just moving beyond phase 1 studies.

Lung Cancer: Sam Janes

PDT using photofrin is approved for treatment of early lung cancer when there are no other therapeutic options. A complete response was achieved in 17 of 29 such patients treated in UCH. Early cancer and pre-cancers can be detected by fluorescence.

The optimum management of high grade dysplasia and carcinoma-in-situ in these patients is not clear. Preliminary results suggest that up to 30% of these lesions regress spontaneously, but these patients are also known to develop multiple, related lesions. There are no randomised trials of treatment for pre-invasive disease. The current weight of evidence (although sparse) suggests that PDT is probably the best of the local treatments that can be delivered endoscopically.

A RCT of PDT v active surveillance is planned using the short acting photosensitizer Fotolon, for pre-invasive disease. The aim is to see if PDT can ablate the index lesion, reduce the rate of local progression and decrease the overall risk of patients developing an invasive cancer, as well as assessing the cost effectiveness and studying the biology of the changes leading to the development of invasive disease. This study is currently seeking funding. An early lung cancer group has been set up between Manchester, Cambridge & UCH to take forward this and other studies.

Oesophageal Cancer: Laurence Lovat

Most recent interest in oesophageal PDT has been in the treatment of high grade dysplasia to prevent progression to invasive cancer. This is NICE approved using the photosensitizer Photofrin, but radiofrequency ablation (RFA) is now usually preferred.

RFA can only treat mucosal disease. PDT may have a role for the primary treatment of small invasive tumours (too deep for RFA) with curative intent, avoiding the need for radiotherapy in patients for whom no curative options remain (relapse after surgery or chemoradiation or unfit even for these treatments). The small risk of missing undetected nodal spread in this group of patients is likely to be acceptable. A potential dose escalation study was outlined.

Palliation of advanced disease using Photofrin is NICE approved but rarely used due to the prolonged skin photosensitivity. This may be reconsidered with newer shorter acting photosensitisers and repeated treatments.

Vascular PDT may help side effects of treatment, such as radiation proctitis.

Bladder Cancer: Joanne Cresswell

The bladder CSG has photodynamic detection (PDD, photodiagnosis) experience rather than direct PDT experience. A NIHR funded study is due to start later this year comparing the clinical and cost effectiveness of white light v Hexvix fluorescence for guidance of TUR for intermediate and high risk non muscle invasive bladder carcinomas, the main end point being time to recurrence. This is planned to include over 500 patients in 20-30 centres around the UK.

No UK trials of PDT in the bladder are currently planned, but could be considered, particularly for non-muscle invasive cancers which are commonly multifocal and may be refractory to conventional treatment. Conventional management of these patients may require total cystectomy.

PDT might be tested in endoscopic treatment of upper tract disease, particularly transitional cell carcinomas. This would require a photosensitizer that could be given systemically rather than intra-vesically.

Colorectal Cancer: David Jayne

Several trials have been undertaken on liver metastases, but there is no evidence that PDT is superior to other local, simpler, image guided interventions such as RFA.

A phase III study of adjuvant PDT after curative resection of colorectal cancers to reduce local recurrence in the post-surgical setting was proposed but never funded.

Bowel cancer screening is detecting more early disease, especially in older patients so increasing the scope for endoluminal surgery such as TEM (transanal endoscopic microsurgery). PDD/PDT may be of value to detect and treat residual tumour and the tumour bed immediately after resection or for later recurrences of rectal cancer.

PDD/PDT might also have a role for detecting/ablating metastatic nodes in patients unfit for abdominal resection and for revisiting peritoneal carcinomatosis. The current MRC supported "Glisten" study shows that after administration of ALA, it is possible to detect fluorescence in metastatic nodes at laparoscopy. A video was shown to illustrate fluorescence in a metastatic node.

AIN (anal intraepithelial neoplasia) comes within the remit of colorectal surgeons as well as dermatologists and may be amenable to PDT. Trials are proposed for this.

Prostate Cancer. Mark Emberton

Focal therapy for localized disease is being tested as a means of avoiding the complications associated with conventional treatment with radical surgery or radiotherapy.

Focal treatment with HIFU (High Intensity Focused Ultrasound) and cryotherapy is not currently proving to be entirely satisfactory.

The current phase 3 clinical trial on vascular-targeted PDT in men with low risk prostate cancer compares PDT with active surveillance. The primary end point is the cancer status at 6 and 12 months from biopsy. A surveillance arm rather than an active treatment was used as the comparator as this was thought to optimise patient recruitment feasibility. 400 patients in 30 centres around Europe have been recruited. Other trials on early prostate cancer offering alternative treatment options have failed to recruit. If the final results are favourable, future studies could consider treating patients with higher risk disease, looking for a reduction in the prevalence of clinically significant disease.

Pancreatic/Biliary Cancer: Steve Pereira

A meta-analysis of PDT for biliary tract cancer suggested possible benefit from PDT, but the quality of evidence was poor.

The negative results of the UK randomised Photostent-2 (biliary) trial (Stenting alone v stenting +PDT) may have been partly attributable to the imbalance of chemotherapy between the study arms. It has been concluded that PDT should only be used for biliary tract cancer in the context of clinical trials, where the treatment arms are balanced for the use of chemotherapy and radiotherapy.

Planned new research studies, in collaboration with Harvard, Dartmouth College and the Cleveland Clinic with NCI funding are on molecular response and imaging-based combination strategies which include light delivery via endoscopic ultrasound guidance, combination of PDT with chemotherapy, and PDT for pancreatic cysts with malignant potential.

Breast Cancer: Mo Keshtgar

PDT for breast cancer is less advanced than in other disease groups. PDT is a possible new minimally invasive, focal therapeutic option. The lack of effect on connective tissue suggests that PDT might result in less deformity of the breast than conventional therapy.

The first clinical trial of PDT in primary breast cancer is treating cancers and a small area of surrounding normal tissue (tissue that would be removed routinely in the subsequent mastectomy) with PDT a few days prior to scheduled mastectomy. The aims are to study the biology of PDT on normal and malignant breast tissue and to correlate the extent of necrosis with the dose of light delivered. MRI scans are taken before PDT and immediately prior to surgery.

Bone tumours: Tim Briggs (presentation by video)

The first UK PDT centre for musculoskeletal disease is underway at the RNOH (Royal National Orthopaedic Hospital). There are two main aims: treatment of recurrent bone & soft tissue tumours and treatment & prevention of infection. New techniques are needed beyond antibiotics for infected prostheses, for which PDT may be an option.

Gliomas: Herbert Stepp

5-ALA fluorescence guided surgical resection of glioblastomas is established as a routine procedure and enables more complete surgical resection. The RCTs in connection with 5-ALA fluorescence guided resection had not been designed to show whether overall survival was improved, and evaluation of the decisive phase III trial failed to reach statistical significance in this regard.

For glioblastomas, a range of clinical studies of PDT, the majority with photosensitizers not based on 5-ALA, have been undertaken and some show anecdotal evidence of benefit, but none so far has had the power to show prolonged survival.

Recent work from Munich using 5-ALA for stereotactic interstitial PDT for glioblastomas has shown encouraging early evidence of prolonged survival, but the numbers so far are small. If the present trend of results continues, a CT for stereotactic PDT could be developed,

Another promising approach is post surgical fractionated PDT, but the amount of evidence currently available is small.

Gynaecological Cancer: Peter Hillemanns

Fluorescence from topical Hexvix can define areas of dysplasia on the cervix. Light (battery operated LED) can be delivered for PDT by a specially designed device that can also both apply Hexvix and can later be removed by the patient (Cevira). 5 hours are required to sensitize the cervix and a further 5 hours for low irradiance light delivery, but during this time, the patient can undertake her normal activities.

Up to 90% response was seen for CIN 2, with 50 % placebo response ($P < 0.01$) and up to 66% clearance of HPV (15% response in placebo group).

A Phase IIb trial is currently under way (250 patients). There have been positive responses from European & North American authorities about undertaking phase III studies. Financial support is needed for a study to include 600-800 women.

PDT for VIN has been shown to be at least as effective as local excision and CO₂ laser vaporization (remission in 60-70%), and not as effective as vulvectomy, but patients much prefer conservative management. PDT is also effective for lichen sclerosis.

5-ALA is effective for fluorescence detection of peritoneal metastases from ovarian cancer.

New developments: Steve Bown

Three fundamentally new developments related to PDT in oncology were described.

1. Photochemical Internalisation (PCI). The principle of photosensitizer plus light is used to break down intracellular membranes (eg on lysosomes) to release chemotherapeutic agents (eg bleomycin) or other biologically active macromolecules trapped in intracellular organelles

2. Tumour immunology. It has been shown experimentally that the breakdown products of cells killed by PDT can act as a vaccine to stimulate an immunological reaction against the original cancer. There is evidence that PCI may markedly enhance the immunological effect.
3. Bioluminescence activated PDT. It has been shown experimentally that light generated chemically (Luciferase + Luciferin, as in fireflies) can kill photosensitized glioma cells transfected with luciferase growing in culture. This has not yet been tested in vivo.

Commercial Perspective

PCI Biotech (Per Walday) and Apocare Pharma (Dirk Huttenberger) gave short presentations providing a commercial perspective on PCI and PDT, highlighting the difficulties they face with the regulatory aspects of treatments that involve both drugs and devices and also the lack of large Pharma industry support. PCI Biotech is starting new PCI studies on cholangiocarcinoma and head & neck cancer with the photosensitizer Amphinex. It was also emphasized that new data indicate that PCI may be used in therapeutic vaccination to dramatically enhance the cytotoxic immune response (antigen specific CD8+T-cells) needed for effective clinical responses. This represents a brand new systemic application of a photodynamic technology. Apocare are undertaking studies with the photosensitizer Chlorin e6 (Fotolon), focusing initially on lung cancer.

Killing Cancer: David Longman

David described the work of Killing Cancer and its origins. Previous donors brought in to fund PDT trials have dropped out because of slow progress that seems to be related to a combination of bureaucracy within hospitals and delays in identifying, assessing and actively including appropriate patients. He is in ongoing discussion with Ministers and officials in the DH about addressing some of the key issues that delay trials.

He asked why protocols are so rigid and inflexible as to not allow re-treatment when the first treatment has produced a significant benefit. All parties involved in clinical trials need to work together to find ways to speed up the bureaucracy and recruitment processes.

David said that he had 'clients' ready and willing to support trials to the value of multiple millions ... but only if future PDT trials are run much more efficiently with patients recruited and processed much more quickly, probably through use of multiple treatment centres.

Outcomes of the Workshop Breakout Sessions

Chairs: Peter Johnson, Matt Seymour

Skin/Gynae/Muco-cutaneous Junctions Group: John Lear

Three studies were proposed;

RCT1: Prevention of SCC in high risk organ transplant recipient patients. Comparing treatment of large field v. no field treatment. Previous studies have shown that the risk of AK's can be reduced, but in those studies, only small areas were treated.

The trial design could compare areas most exposed to light within individual patients (eg treat one arm and not the other) or randomise between patients (treatment or no treatment for an area such as the head & neck), with the primary outcome being the development of SCC at 1, 3 and 5 years and secondary outcomes being cost effectiveness and PROMs (Patient Related Outcome Measures).

RCT2: BCC and the treatment of multiple lesions. Four arm trial design - PDT v Imiquimod v Excision v Curettage. Trial Outcomes – Efficacy, Health Economics and PROMs

Requirements to consider – Consumer input required to assess patient acceptability for randomisation – would they find it acceptable to undergo a more complex treatment via PDT verses excision, which already confers a high cure rate but which may have a less attractive cosmetic result, especially on areas like the head & neck. It would be necessary to stratify between different types of BCC eg superficial vs. nodular.

Phase I/II study VIN – the efficacy and response rates using second generation photosensitizing agents. In due course, RCT's could compare PDT with imiquimod, local excision and CO2 laser as well as looking at various combinations of these treatments to consolidate the comparisons presented in the morning session.

It was suggested that these options be discussed further with the Gynae Clinical Studies Group and considered for incorporation with the CIN group.

Other possibilities would address hedgehog inhibitor pathway studies

The value of a centre for co-ordinating skin PDT studies was emphasized, as described in the morning session. This would be a good forum for clinicians with good ideas but no time to air their thoughts for discussion.

Head & Neck Group: Bing Tan

Proposed studies:

Questionnaire. Circulate a questionnaire capturing the perception of PDT within the Head & Neck Clinical community and willingness to participate in multi-centre clinical trials.

There has been so much discussion of the value of PDT for head & neck cancer that our first proposal is to circulate a questionnaire capturing the perception of PDT within the Head & Neck Clinical community. Issues highlighted from the questionnaire could then be targeted to improve the perception of PDT prior to setting up RCT's.

RCT1: Non-inferiority study of Surgery vs. PDT in early oral cancer. Great care needed to define patient inclusion criteria, end points and PROM's.

Acceptability for patients will need to be addressed by canvassing consumer groups as part of study development. Additionally the development of a questionnaire/survey for surgeons treating early cancer should be undertaken to gauge their support for this trial proposal. The protocol will need to define the type of patient suitable for inclusion. Early, primary lesions in readily accessible parts of the mouth will best be treated by simple excision. Those suitable for a RCT of surgery v. PDT will most likely be those with lesions in less accessible sites or sites where the scar after surgery might cause functional or cosmetic problems, be persistent or recurrent lesions after previous treatment with surgery or radiotherapy, or be in patients with field change disease. The primary endpoint would be a complete response, measured by histology & imaging, as appropriate for individual cases, but a longer term aim would be the incidence of uncontrollable recurrent disease.

Consideration for the definition of treatment failure was discussed along with how treatment recurrence will be dealt with within the trial – in either arm, should patients have the same treatment again or have an alternative treatment? It will also be essential to define PDT treatment conditions carefully to be sure it is used optimally to reduce the risk of technical failures due to incomplete treatment.

RCT2: RCT for end stage disease - Palliative chemotherapy v. PDT + chemotherapy *or* PDT v. palliative chemotherapy *or* crossover study.

In view of the likely toxicity of chemotherapy, could this be a crossover study? Initially PDT v chemotherapy with crossover after 6-8 weeks if the first treatment is ineffective, so the side effects of PDT in advanced disease could be distinguished from those related to the chemotherapy.

The current photosensitiser is Foscan, although it was highlighted that newer drugs may have less side effects, particularly a considerably shorter period of generalized skin photosensitivity.

Lung/Oesophagus/Bladder Group: Laurence Lovat

Lung

RCT of PDT v active surveillance for pre-invasive disease in the major airways

The main proposal is for the RCT of PDT v active surveillance for pre-invasive disease in the major airways as described by Sam Janes in his presentation this morning. This is currently not funded as his recent application to NIHR was not successful.

Oesophagus

Phase I/II study of PDT for localised recurrence after first line treatment, followed by a non-inferiority study of PDT v standard treatment (stent/RT/chemo).

The need is for a pragmatic trial design due to the types of recurrence requiring alternative control arm treatments as per standard. The main endpoints would be quality of life at all times after treatment and duration of symptomatic relief. It may be appropriate to consider an arm that is a combination of PDT with a standard treatment. At some point in the future, if this study goes well, it may be worth considering PDT as primary treatment for early invasive cancers with no evidence of spread beyond the oesophageal wall in patients who are not fit for conventional definitive treatment.

Bladder

A NIHR funded RCT is due to start later this year comparing the clinical and cost effectiveness of white light v Hexvix fluorescence for guidance of TUR for non-muscle invasive bladder carcinomas, the main end point being time to recurrence.

Jo Cresswell plans to take back to the bladder CSG the information gained from the day, particularly with regard to non-muscle invasive refractory patients requiring cystectomy, for discussion of possible future PDT studies. She has made links with German counterparts who are developing trials within this area.

Colorectal/laparoscopy: David Jayne

Three ideas were proposed:

RCT: TEM (Transanal Endoscopic Microsurgery) with and without adjuvant PDT for excision of small rectal cancers to reduce the incidence of local recurrences.

TEM is becoming more popular for early rectal cancers, but full thickness excisions leave an open wound where exfoliated cells may implant. The recurrence rate after these procedures is about 20%. The trial proposal is to establish if PDT can reduce the recurrence rates associated with this new technology.

Nested within the trial could be a photo-diagnostic element, which may help to define the tumour extent and establish if the local excision has been complete.

The attractions are that there is an established community of people doing TEMs, there is a large registry of patients, no conflicts and TEM is future proofed (new technology won't be out of date by the end of the trial). Furthermore results will be obtained quickly as local recurrence usually occurs within 12 months.

Phase I/II Study: AIN - the efficacy and response rates using second generation photosensitizing agents.

Previous experimental work showed that anal mucosa and peri-anal skin could be ablated and treated areas healed by regeneration with minimal scarring and no damage to sphincters. Topical photosensitizer application in AIN patients shows promise as a photo-diagnostic to outline the extent of disease. There have only been isolated case reports of treating AIN. It is acknowledged that proof of concept is required and that it would be appropriate to identify several centres to do this prior to planning any RCT's.

There are many similarities between AIN and CIN, VIN and PIN (penile intraepithelial neoplasia) and that trials of PDT for each of these would be worth co-ordinating, especially

as all except CIN are relatively rare. This study should be discussed with the dermatology, urology (for PIN) and gynae (for VIN) CSG's.

Phase I/II study: Detection of metastatic nodes at laparoscopy with ALA-fluorescence.

It has already been demonstrated that metastatic nodes can be detected by this technique, but further work is needed to explore the value of PDD and PDT in this situation.

Pancreas /Breast: Mo Keshtgar

Pancreas

Phase II study of PDT for locally advanced pancreatic cancer with light delivery under direct endoscopic ultrasound guidance

Phase I/II study combining PDT with chemotherapy for locally advanced pancreatic cancer

Following the recent phase I study on inoperable but localized pancreatic cancer showing the safe production of necrosis in the tumour, the next planned stages are delivery of light under endoscopic ultrasound guidance and combining PDT with chemotherapy. These are not yet ready for phase 3 studies, but in due course a RCT comparing chemo-(radio)-therapy with chemo-(radio)-therapy + PDT for locally advanced cancer could be developed with the Pancreatic CSG subgroup led by Stephen Falk.

Phase II study of PDT for pancreatic cysts

The proposal is for PDT to be added as a mirror to the current trial looking at radiofrequency ablation for pancreatic cysts with malignant potential with the possibility in the future to have RFA as a comparative arm in a RCT.

Breast

Two proposals were outlined:

Phase I/II Multifibre trial for larger tumours with RT to the margins.

Multi-fibre PDT might be suitable for patients with larger cancers, the procedure being followed by RT to cover the tumour margins.

Phase I/II Single fibre PDT with smaller tumours (1-2cm) that are hormone responsive with hormone treatment after PDT.

At a later stage, it might be possible to devise a RCT of PDT + hormones v surgery + hormones, particularly in older women. The primary endpoint would be local control, with secondary outcome on cosmetic and quality of life considerations.

The Breast CSG chair (Dan Rae) commented that further results from Mo's trial are needed along with a suitable validation phase with surgical resection, so more early phase trials should be undertaken.

Brain Group: Herbert Stepp

RCT of stereotactic, interstitial PDT of glioblastoma v. a conventional surgical option (to be defined) if trend of benefit in current stereotactic trial continues. Collaboration with Munich team.

Discussion on future studies was limited as neither the planned neurosurgeon nor the brain cancer CSG representative was able to attend. The encouraging early results from the phase 1 study outlined in the morning on stereotactic interstitial ALA-based PDT for Glioblastoma already underway in Munich were highlighted and the potential for international collaboration was offered, co-ordinated by Herbert Stepp. His group is planning collaborative work on both refining clinical treatment techniques and pre-clinical topics. Some further follow up of the current clinical study is required, but it is hoped that relatively soon it will be possible to define a treatment regimen that can be tested against conventional management. A major challenge will be to identify a suitable operable patient group as a comparator for a randomised study.

There is interest from PCI Biotech in exploring PCI for brain tumours and expressions of interest are invited. Another suggestion was to explore the release of anti-oxidant inhibitors in the brain

Industry Group: Paul Jones CRUK drug development office

There was further reiteration of the significant regulatory hurdles industry faces due to PDT requiring both medical device and medical product approvals. There was much discussion about how PDT can become profitable in a reasonable period of time.

It was emphasised that if the evidence base improves, large pharmaceutical companies are likely to increase their interest and may consider taking over the small companies currently active in the field. One or two good trials could rapidly set the ball rolling to achieve this.

Closing Remarks

Peter Johnson commented that PDT falls into broadly two categories: Early stage disease and advanced stage disease. There have been technological advances within the PDT area both in drug development and light delivery resulting in new research opportunities. He said that trials do not necessarily have to be fully funded by pharma, but it is usually essential that there is close collaboration with pharma so any drug is supplied free or at reasonable cost.

Useful and interesting ideas for concepts have been developed today to take to CSG's to develop further. The initiative was placed with the meeting delegates to engage with CSG's to continue the momentum of this work and to cement relationships created from today and forge new ones.

Matt Seymour commented that possibilities for 12-13 trials had been outlined during the meeting, 10 of which were basically new ideas and that he was determined that action should come out of the meeting. For each trial, an enthusiast must be identified to formulate a study and present that to the relevant CSG. Hopefully, at least 3-4 will progress to the stage where they can apply to one of the major funders in their next round.

30th August 2014