# Supplementary Materials: Oncologic Photodynamic Therapy: Basic Principles, Current Clinical Status and Future Directions

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**Table S1.** Summary of clinical studies reviewed.

| Lung | Study Goal | Study Method | PS | Study Outcome | AEs | Reference |
|---|---|---|---|---|---|---|
| Endobronchial non-small cell lung cancer | Palliative treatment | Multimodal PDT with HDR ($n$ = 9) | Photofrin® | Prolonged local tumor control in 89% | Bronchial contraction | [132] |
| Advanced non small cell lung cancer with central airway obstruction | Palliative treatment | Multimodal PDT with CT, RT or CRT ($n$ = 10) | talaporfin (NPe6) | CR 20%, PR 70%, NR 10%; Mean FEV1 1.70 ± 0.69 L before and 1.99 ± 0.60 L after PDT ($p$ = 0.029); 1-year survival 70% with PDT vs. 35% with CT as stated in literature | Mild itching | [133] |
| Stage IIA-IV intractable non small cell lung cancer | Palliative treatment | Multimodal PDT with CT ($n$ = 12) | talaporfin (NPe6) | Median stenosis rate pre-PDT was 60%, one week post-PDT 15% ($p$ = 0.0003) and one month post-PDT 15% ($p$ = 0.0016); PDT improved FVC (1.93 vs. 2.58 L) and FEV (1.28 vs. 1.67 L); Improved QoL and opening of bronchial lumen in all patients | No PDT related morbidity or mortality | [135] |
| Stage IIIA and IIIB central non small cell lung cancer | Improve tumor resectability with PDT | Pre-operative CT in some cases PDT ($n$ = 42) | talaporfin (NPe6) | CR 33% after CT + PDT vs. 10% after CT ($p$ = 0.054); Radical resection in 89% of operable patients after CT + PDT vs. 54% after CT ($p$ = 0.038) | Hemoptysis | [136] |
| Lung cancer or thymoma with pleural spread | Postoperative treatment | Postoperative PDT vs. standard care (CT or RT) ($n$ = 18) | Photofrin® | 3- and 5-year survival rate were 68.9% and 57.4% respectively. Median OS of 39 months after PDT vs. 17.6 months after CT or RT ($p$ = 0.047) | Erythema, air leakage from lungs | [137] |
| Stage II-IV intractable bronchial lung cancer with lumen obstruction | Palliative treatment | Standalone PDT ($n$ = 30) | Photofrin® | OR 86.7% with CR 13%, PR 73%, MR 13%. Mean obstruction % decreased from 90% to 16.7% | Increased phlegm, secretions, mild pain, photosensitivity with local redness, swelling and scurf | [139] |
| Centrally located early lung cancer with lesions < or >1 cm | First-line treatment | Standalone PDT for lesions > or < 1 cm ($n$ = 75) | talaporfin (NPe6) | CR in 94% of lesions ≤1 cm and 90.4% of lesions ≥1 cm ($p$ = 0.368); NPe6 proved more effective for lesions >1 cm compared to Photofrin® in earlier studies | Not reported | [142] |

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| Multiple primary lung cancers | First-line treatment | PDT alone or combined with surgery (*n* = 39) | talaporfin (NPe6) | CR was 100% for lesions treated with PDT alone or with surgery + PDT | Not reported, no skin photosensitivity after 2 weeks | [143] |
| Carcinoma in situ and microinvasive carcinoma of the central airways | First-line treatment | Light-dose ranging study (*n* = 17) | HPPH | Overall response after 1-month CR 82.4%, NR 17.6%. After 6-months CR 72.7% | Mucus plugs, coughing, mild pain, erythema, photofobia | [145] |
| Malignant pleural mesothelioma | Retrospective study of multimodal treatment | Lung sparing operation followed by intraoperative PDT (*n* = 38) Median FU 34.4 months | porfimer sodium | 37/38 (97%) Macroscopic complete resection of stage III/IV using lung sparing surgery Median survival 31.7 months, Median progression-free survival 9.6 months | Not reported | [138] |
| **Esophagus** | **Study Goal** | **Study Method** | **PS** | **Study Outcome** | **AEs** | **Reference** |
| High grade dysplasia in Barrett's esophagus, adenocarcinoma and squamous cell carcinoma | First-line treatment | Standalone PDT or combined with adjuvant RT and CT (*n* = 50) | Photofrin® | CR without recurrence was seen in 32%, 30% alive with recurrence, 38% died of recurrence or other causes | Esophagal strictures, mild photosensitivity and pleural effusions. | [152] |
| Barret's esophagus with high grade dysplasia, intramucosal carcinoma, or T1 cancer | Palliative treatment | PDT with continued use of proton pump inhibitor (*n* = 116) | Photofrin® | At 12 months post-PDT, 70% was HGD and carcinoma free. Complete ablation of BE was achieved in 39% | Not reported | [153] |
| High grade dysplasia in Barrett's esophagus and mucosal carcinoma | First-line treatment | Light and PS dose-ranging study (*n* = 11) | Photofrin® | CR was seen in 45%, 45.5% had recurrence and 9% was undertreated with residual disease | Esophagal strictures | [154] |
| High grade dysplasia in Barrett's esophagus and mucosal carcinoma | First-line treatment | PDT with continued use of proton pump inhibitor and EMR (*n* = 126) | Photofrin® | Three months after PDT, 40% had no or nondysplastic BE and 60% were considered non-responders | Not reported | [155] |
| High grade dysplasia in Barrett's esophagus and mucosal carcinoma | First-line treatment | PDT with EMR (*n* = 31) | Photofrin® | No evidence of HGD was seen in 77% during follow up. Of this group, 8.3% had recurrence 9 months post PDT | Not reported | [156] |
| Advanced obstructing esophageal cancer | Palliative treatment | Multimodal PDT with RT and stenting (*n* = 20) | Photofrin® | Improved dysphagia scores were reported in 90% of patients. Median OS was 7 months with one patient achieving CR lasting 28 months post-PDT | Esophageal stricture (*n* = 2), skin pigmentation (*n* = 3), and facial edema (*n* = 1) | [157] |
| High grade dysplasia in Barrett's esophagus | First-line treatment | PDT with continued use of proton pump inhibitor and EMR (*n* = 129) | Photofrin®or HPD | After 1 and 3 years post PDT, CR was 88% and *6% respectively. Of initially failed responses, 70% achieved CR following retreatment. Carcinoma developed in 6.2% | Strictures (27%), Photosensitivity (60%), blistering (7%) | [161] |

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| High grade dysplasia in Barrett's esophagus | Salvage treatment | Standalone PDT ($n$ = 21) | Photofrin® | Of 19 patients included in the follow-up, CR was achieved in 16 with a 5-year DSF of 84%. Significant reduction in the length of Barrett's segment post PDT ($p$ = 0.035) | Photosensitivity ($n$ = 2), strictures ($n$ = 7), chest pain, vomiting | [162] |
| High grade dysplasia in Barrett's esophagus and adenocarcinoma | First-line treatment | Standalone PDT ($n$ = 125) | Photofrin® | CR was 71.9% of the PDT group. Cumulative occurrence of recurrence was 49.7% | Photosensitivity (10.4%), strictures (10.4%), nausea and vomiting | [163] |
| High grade dysplasia in Barrett's esophagus | First-line treatment | Dose-ranging study PDT with EMR ($n$ = 16) | 5-ALA | For 30 mg/kg ALA, 25% achieved succesful treatment compared to 100% of 60 mg/kg group with red light and 16.6% for green light. PD was 4% in the optimal dose group | Mild photosensitivity ($n$ = 1), gastrointestinal bleeding ($n$ = 2), odynophagia and chest discomfort (40%) Nausea and vomiting, pneumonia ($n$ = 4) | [164] |
| High grade dysplasia in Barrett's esophagus | First-line treatment | Standalone PDT ($n$ = 64) | 5-ALA or Photofrin® | CR achieved in 16/34 (47 %) and 12/30 (40 %) for 5-ALA and Photofrin® respectively ($p$ = 0.34). For lesions <6 cm ALA-5 performed better ($p$ = 0.02) but no difference was seen for bigger lesions ($p$ = 0.37) | AE after Photofrin® vs. 5-ALA: strictures (33% vs. 9%) and photosensitivity (43% vs. 6%) | [165] |
| High grade dysplasia or early intramucosal adenocarcinoma of esophagus | First-line treatment | Light- and drug-dose ranging study ($n$ = 36) | HPPH | Initial CR was 100% with optimal dosage. The 1-year CR rate across all treatment regimens was 72% (13/18). Of 13 patients with CR, 7 (54%) did not show recurrence on follow-up at 5 years | Photosensitivity, mild to moderate chest pain with one case of severe pain, dysphagia, nausea, odynophagia, strictures ($n$ = 3), pleural effusions($n$ = 4) | [166] |
| Early squamous cell carcinoma without metastasis | Salvage treatment | Standalone PDT ($n$ = 9) | talaporfin (NPe6) | CR achieved by 5 out of 9 patients (55.6%) | Mild fever ($n$ = 1), dysphagia ($n$ = 1), pain ($n$ = 3) | [167] |
| Early squamous cell carcinoma without metastasis | Salvage treatment | Standalone PDT ($n$ = 25) | Photofrin® | CR in 19 of 25 patients (76%), 3-year PFS and OS rates were 40% and 38.4% respectively | Chest pain ($n$ = 15), pharyngeal pain ($n$ = 4), dysplasia ($n$ = 10), mild fever (12) and photosensitivity ($n$ = 8), stenosis requiring dilatation ($n$ = 6), death by aortic-esophageal fistula ($n$ = 1) | [168] |

| Skin | Study Goal | Study Method | PS | Study Outcome | AEs | Reference |
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| Carcinomas of the breast, colon, prostate, squamous cell, basal cell, and endometrium; malignant melanoma; mycosis fungoides; chondrosarcoma; and angiosarcoma | Explorative | Explorative (*n* = 113) | HPD | 111 out of 113 responding complete or partial<br>All types are responding | Prolonged skin photosensitivity | [12] |
| NMSC: BCC, AK, Bowens, SCC | Review | | Photofrin®, ALA, Metvix®, Levulan®, | BCC (n + s): 85% with Photofrin®<br>sBCC: 92% with ALA<br>nBCC: 71% with ALA<br>AK: 75–90% levulan<br>Bowens: 95% CR at 10 months Photofrin®, 90% at 15 months ALA<br>SCC: > 50% ALA<br>(compiled data of 14 studies) | | [171] |
| BCC, SCC, nodules of carcinoma of the breast, AK | Explorative | Explorative | ALA | BCC (*n* = 80): 90% CR, 7.5% PR, 2.5% NR, 2–3 months FU<br>In-situ or early invasive SCC (*n* = 6): All CR<br>SCC >10 mm (*n* = 2): PR<br>AK (*n* = 9): 9 CR | Not reported | [172] |
| NMSC | Review | Different pretreatments | ALA and MAL | Simple pre-treatments or additions to the regular practice of PDT improve clinical outcome | Not reported | [173] |
| nBCC | Curative treatment | Debulking vs. no debulking<br>8 weeks FU histo<br>Pain visual analougue scale (*n* = 43) | ALA vs. MAL | *n* = 22 vs. 21<br>No difference both groups had 6 residual tumor<br>Costs of MAL 6 times higher | Not reported | [176] |
| AK, BD, nBCC, sBCC | Curative treatment | Gentle (AK, BD, sBCC) or debulking curettage (nBCC) 3 h cream, ill aktilite 37 J/cm² Repeated within few weeks for BD, sBCC, nBCC (*n* = 203 in 116 patients) | ALA vs. MAL | ALA vs. MAL: %CR (n)<br>AK: 63% (24) vs. 75% (44)<br>BD: 89% (9) vs. 78% (18)<br>nBCC: 84% (19) vs. 84% (25)<br>sBCC:88% (25) vs. 87% (39) | Not reported | [177] |

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| sBCC | Multicentre, randomised, controlled, open study | PDT vs. surgery<br>MAL: 2 sessions, 7 days apart, repeated after 3 months if needed or surgery<br>3 h cream, ill aktilite 37 J/cm²<br>(*n* = 196 patients, 1.4 lesions/paient)<br>12 months FU | MAL | CR after 3 months<br>92.2 % MAL, 99.2% Surgery<br>Recurrence after 12 months<br>9.3% MAL, 0 Surgery<br>CO excellent/good<br>94,1% MAL, 59,8% surgery | MAL: 37/100 65 related AE<br>Surgery: 14/96 21 related AE<br>Most AE were expected of dermatological nature and all were mild or moderate<br>21 serious AE non related | [178] |
| sBCC | Single blind, non inferiority, randomizsed controlled trial | PDT vs. Imiquimod vs. Fluorouracil<br>(*n* = 583 patients)<br>12 months FU | MAL | 26 lost to FU<br>Recurrence-residue:<br>MAL: 52/196<br>Imi: 31/189<br>5 fu:39/198<br>Imi vs. MAL $p = 0.021$<br>CO (good-excell): 62.4% MAL, 61.4% imi, 57.5% 5-FU, no diff.<br>Compliance: 100% Mal, 20.9% imi, 31.3% 5-FU | MAL: no AE<br>Imiquimod: 1 patient<br>Fluorouracil: 2 patients<br>Local wound infection | [179] |
| sBCC | Randomized prospective trial | Single vs. light fractionation<br>(*n* = 745)<br>5 year FU | ALA | 88.4%CR fractionated PDT<br>75.4%CR Single ill | Not reported | [180] |
| sBCC | Explorative: Pain reduction through low-high fluence rate illuminations | Low fluence rate illumination until photobleaching reached to 90% followed by high FR ill till 200 J/cm²<br>(*n* = 33 in 26 patients) | ALA | Fluence to 80% fluorescence at 10, 20, 40, 50, 60 and 150 mW/cm² was 5.7, 4.5, 7.5, 7.4, 12.4, and 28.7<br>No sign pain with FR < 50 mw/cm²<br>CR comparable to continuous treatment | Not reported | [181] |
| sBCC | Prospective study on pain control | Low fluence rate illumination until photobleaching reached to 90% followed by high FR ill till 200 J/cm²<br>(*n* = 25 sBCC)<br>FU to 24 months | MAL | First 40 or 50 or35 mW/cm² than 70 mW/cm² to 75 J/cm²<br>Pain increased with increasing irradiance. And cr decreased. | Not reported | [182] |

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| AK | Randomized, double-blind, prospective study | Split-scalp curative comparative study<br>Pain assessment<br>($n$ = 15)<br>FU 1 months | ALA 5 h vs. MAL 3 h | Reduction of lesions<br>6.2 ± 1.9 ALA<br>5.6 ± 3.2 MAL<br>No sign diff.<br>Sign. More pain with ALA<br>Pt preference MAL | | [183] |
| AK on the scalp | Comparative study | Waldman 100 J/cm² at 160 mW/cm²<br>($n$ = 69) | ALA vs. MAL | 54% discontinued ALA treatment<br>14% discontinued MAL treatment | | [184] |
| AK | Multicentre, randomised, observer-blind phase III trial | PDT vs. placebo<br>($n$ = 571)<br>3 months FU<br>Max 2 times PDT 3 months apart | BF-200 ALA vs. MAL | CR BF-200 ALA: 78.2%<br>Plac.: 17.1% $p < 0.0001$<br>MAL:64.2% $p < 0.05$<br>Lesion CR, BF: 90.4%<br>MAL: 83.2%, Placebo.: 37.1%<br>Analysis of subgroups (grade, target areas) showed sign better BF-200 than MAL/Placebo | No difference in related EA MAL vs. BF-200 ALA (application site erythema, burning and pain)<br>Narrow spectrum devices—more and worse AE | [185] |
| AK | Multicentre, randomised, observer-blind phase III trial | FU of 2 phase II studies<br>($n$ = 630)<br>6 en 12 months FU | BF-200 ALA vs. MAL | Proportion that remains completely clear: (in favour of)<br>47% BF-200 vs. 36% MAL<br>No safety concerns | 5 related AE in (patients):<br>SCC (1), BF-200 ALA (2), BCC (2), MAL (1) Bowens (1) MAL, Placebo (1) | [186] |
| AK | Retrospective monocentric Study Pain | Superficial curettage, Ibuprofen, 3 h cream, ill aktilite 37 J/cm²<br>VAS pain score during and 8 h post ($n$ = 173 patients, 965 lesions) | MAL vs. BF-200 | MAL vs. BF-200 during VAS score: 5 vs. 5.8 $p < 0.001$<br>Treat. Interupt: 13.2 vs. 19.9% $p < 0.001$<br>Severe pain: 25 vs. 36% $p < 0.05$<br>No difference at 8 h | Not reported | [187] |
| AK | Randomized, double blind, prospective study | Split-face<br>Grade I: 1 PDT session<br>Grade II-III: 2 PDT sessions ($n$ = 13 patients, 177 AK)<br>3 months FU | BF-200 ALA vs. MAL | BF vs. MAL<br>Complet clearance rate 84.5% vs. 74.2% $p = 0.099$<br>No difference in reduction grading $p = 0.065$<br>Per patient half-face analysis BF sign better CR grade I $p = 0.027$<br>No preference | Nearly painless and no difference in adverse reactions | [188] |

| Head and Neck | Study Goal | Study Method | PS | Study Outcome | AEs | Reference |
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| Leukoplakia or erythroplakia | First-line treatment | Standalone PDT ($n$ = 147) | temoporfin or 5-ALA | CR was achieved in 77.6% after first treatment. At the 5-year follow-up CR was 78.9%. At time of writing CR was 81% while 7.5% had PD, 3.4% SD and 8.2% PR | Mild to moderate pain and skin photosensitivity | [201] |
| Oral squamous cell carcinoma | First-line treatment | Standalone PDT ($n$ = 38); repeated when disease reoccurred 6–7 months after 1st PDT | temoporfin | CR was 68.4% at last review. Overall recurrence of the disease was 15.8% (6/38); and 5-year survival was 84.2%. | Pain, photosensitivity with six patients who failed to avoid direct sun exposure having 1st ($n$ = 2), 2nd ($n$ = 3) and 3rd ($n$ = 1) degree sunburns | [202] |
| Local persistant and recurrent nasopharyngeal carcinoma | Salvage treatment | Standalone PDT ($n$ = 21) | temoporfin | CR was 95% 10 weeks post-PDT. The unresponsive patient 27 months after initial PDT. Two year PFS was 49% with regional relapse ($n$ = 6) and distant metastasis ($n$ = 5) observed. Mean two year OS was 65%. | Local pain | [208] |
| Early head and neck squamous cell carcinoma | First-line treatment | PDT vs. Surgery ($n$ = 243) | temoporfin | CR of 86% for T1 and 63% for T2 tumors after PDT ($p$ = 0.005) compared to 76 % for T1 and 79% for T2 after surgery ($p$ = 0.75). LDFS after PDT was 102.6 and 113.8 months for T1 and T2 tumors respectively compared to surgery with 152.7 and 152.8 months for T1 and T2 tumors respectively. Mean OS was 101.5 and 116.9 months for PDT treated T1 and T2 tumors respectively ($p$ = 0.842). After surgery mean OS was 122.6 months for T1 and 109.5 months for T2 tumors ($p$ = 0.450) | Not discussed | [207] |
| Early head and neck cancer | First-line treatment | PDT vs. Surgery ($n$ = 98) | temoporfin | After one intervention, rate of local control was 89% (49/55) after PDT and 74% (32/43) after surgery ($p$ = 0.07). Including subsequent interventions, 5 year local DFS was 67% and 74% for PDT and surgery respectively. Overall 5 year DFS was 47% for PDT and 53% for surgery. Five year OS was 83% for PDT and 75% for surgery | Not discussed | [206] |

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| Oral squamous cell carcinoma or mucosal dysplasia | First-line treatment | Standalone PDT ($n$ = 25) | Photofrin® | Of 18 OSCC patients, 17 achieved CR and 1 PR. CR was 100% for dysplasia patients. Recurrence was observed in both the OSCC ($n$ = 2) and dysplasia ($n$ = 1) group. Disease specific survival was 95.8% | Swelling, oedema, (sometimes severe) pain, phototoxic skin reactions, skin discoloration | [194] |
| Early head and neck squamous cell carcinoma and dysplasia | First-line treatment | Light-dose ranging study ($n$ = 40) | HPPH | Only the 140 J/cm$^2$ group was used for response ratios; CR for dysplasia was 46% and for OSCC 82% ($p$ = 0.056) although dysplasia responses were less durable | Pain and oedema (100%), grade III oedema, mild sunburns ($n$ = 4) | [197] |
| T1 Oropharynx | First clinical study | 48 h drug-light 100 J/cm$^2$ at 100 mW/cm$^2$ ($n$ = 42 patients) 2 months biopsy | HPD | CR 40 (95%) Recurrence 1 Residual 1 | Not reported | [192] |
| Various cancers | Explorative | Explorative 1 year FU | mTHPC PII (1 patient) ALA (1 patient) | Good clinical responses | | [195] |
| Tis-2, face, oropharynx, larynx | Prospective clinical study | 48 h drug-light 100 J/cm$^2$ at 100 mW/cm$^2$ ($n$ = 83 patients) 2 months biopsy | Photosan III® | 51 of 57 BCC, 6 of 7 SCC skin, 6 of 7 Oro CA 11 of 12 larynx CA Complete histological FU 13–71 months | Not reported | [193] |
| Carcinoma of the lip SCC | Non-randomized phase II study | 0.15 mg/kg 96 h drug-light 20 J/cm$^2$ at 100 mW/cm$^2$ ($n$ = 25 patients) 12 weeks FU biopsy | Foscan® | 24/25 = 96% CR 12 weeks 2 recurrences (4,18 months) Lymphnode meta 7 months CO better than surgery | Swelling, local pain Photosensitivity in 5 patients | [204] |
| All kinds of cancer Not just H & N | review | review | | Endoscopic light delivery Interstitial light in buried tumors that would require extensive surgical resection Adjuvant therapy after removal of bulk tumor | | [199] |
| Oral cavity and oropharynx | Prospective study | 0.15 mg/kg 96 h drug-light, nasotracheal intubation ill ($n$ = 25 patients-29 T1-T2 NO) 37 months FU | mTHPC | 25 (86%) CR 4 recurrent lesions had conventional therapy | No permanent impairment of mastication, swallowing and articulation of speech | [196] |

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| Persistent or recurrent H & N cancer unsuitable for surgery, radiotherapy or chemo | Phase I-II Salvage treatment | 0.15 mg/kg 96 h drug-light Interstitial PDT 20 J | mTHPC | 45 patients, 9 CR, 5 10–60 months 24 Sympt relief, Median survival 16 months in 33 responders Median surv 2 months in 12 nonresponders | Carotid blow out at 2 weeks post PDT | [200] |
| Recurrent respiratory papillomatosis Needed surgery every 3 months | Parallel-arm, randomized trial | Single PDT 6 days drug-light 80–100 J adult/60–80 J child ($n$ = 15 patients + 2); 12 months FU | mTHPC | 5 remission with recurrences at 3–5 years Tracheal disease not responsive No change prevalance latent pap virus DNA | Not reported | [203] |
| Various deep-seated H & N region upper and lower limbs | Prospective study | 0.15 mg/kg ($n$ = 68 patients) 7 months FU | mTHPC | 2 patients free of disease Half patients good responses A third moderate resp. 6 weeks FU radiological: 13 patients no response, 18 patients minimal, 23 moderate 11 sign. Resp. | A range of AE reported in number not in severity | [209] |
| Oral SCC and fieldcancerisation | Light dose ranging study | 0.15 mg/kg 72–96 h drug-light ($n$ = 20) | mTHPC | 12*single lesions < = T3 cleared all 6 T4 3 out of 6 cleared T1 + T2: 9 of 14 cleared (field cancerization) | Not reported | [205] |
| Paranasal sinuses Scc, adenocarcinoma, undiff. Carcinoma, adenoid cystic carcinoma, risarcoma | Adjuvant therapy to surgery | Open and endoscopic approach ($n$ = 15) | mTHPC | Macroscopic resection $n$ = 3 Debulking surgery $n$ = 12 $N$ = 5: CR | No AE $N$ = 4: Temporary diplopia $N$ = 1: ext. necr. Oro-nasal fistula | [213] |
| Sino-nasal malignancies | Retrospective analysis | PDT ($n$ = 7) | mTHPC | No CSF leakage, meningitis or major bleeding. Temporary diplopia in 3 patients, facial edema and pain in all patients | | [212] |
| **Bile Duct** | **Study Goal** | **Study Method** | **PS** | **Study Outcome** | **AEs** | **Reference** |
| Bile duct cancer | Salvage treatment | Multimodal PDT with adjuvant CT or RT ($n$ = 7) | talaporfin (NPe6) | CR without recurrence in 3 of 7 patients. Two deaths by liver metastasis. One cancer-unrelated death and one is still alive with cancer | Biliary stenosis ($n$ = 1), transient epithelial or peribiliary inflammation ($n$ = 2), mild transient cholangitis ($n$ = 1), mild photodermatitis ($n$ = 2), skin pigmentation ($n$ = 1) | [218] |

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| Bile duct cancer | Palliative treatment | Biliary stenting with PTD (*n* = 170) vs. stenting alone (*n* = 157) | Photofrin® | Increase in length of survival, improvement of Karnofsky scores and decrease of serum bilirubin after PDTtreatment were observed | Biliary sepsis (15%), Skin phototoxicity (6%) | [217] |
| Bile duct cancer | Palliative treatment | Standalone PDT (*n* = 11) | Foscan® | Median survival was 18 months after PDT. Four patients showed tumoricidal depth of >7.5 mm and prolonged relief of cholestasis and jaundice. QoL improved in 6 of 11 patients. | septic cholangitis, recurrent liver abscess, skin photosensitivity, cholangitis | [220] |
| Bile duct cancer | Palliative treatment | PDT plus stenting (*n* = 29) | Foscan® | Median time to local tumor progression was 6.5 months, fewer PDT treatments needed, Median survival time was 15.4 months | cholangitis (*n* = 4), liver abscess (*n* = 2), cholecystitis (*n* = 2), phototoxic skin (*n* = 5), and injection site reactions (*n* = 7) | [221] |
| Bile duct cancer | Palliative treatment | Endoscopy-guided PDT using porfimer (*n* = 12) and talaporfin (*n* = 13) | Porfimer and talaporfin | Higher cytocidal effect with talaporfin than that of porfimer after PDT. Less Phototoxicity caused by talaporfin and therefore staying at hospital after PDT was shorter | Photosensitivity | [225] |
| Bile duct cancer | Palliative treatment | Endoscopic ultrasound-guided PDT using Photolon (*n* = 4) | Photolon® | The median volume of necrosis was 4 $cm^2$, Disease remained stable during a median follow-up of 5 months | No treatment-related mortality or complications | [226] |
| Unresectable hilar carcinoma | Palliative treatment | PDT combined with stenting (*n* = 13) | Foscan® | Five out 13 patients died within 13 months post-PDT. Eight patients had a median survival time of 13 months and were still in follow-up at time of writing the paper | Abdominal pain, nausea | [222] |
| Unresectable hilar carcinoma | Palliative treatment | PDT + CT vs. PDT alone (*n* = 43) | Photofrin® | Median OS of 8 months for PDT vs. 17 months PDT+S-1 arm. One-year survival was 32% and 76.2% respectively. PFS was 2 months vs. 10 months respectively | Liver abscess (*n* = 3), photosensitivity (*n* = 4), cholangitis (*n* = 4) | [223] |
| Unresectable hilar carcinoma | Palliative treatment | PDT + CT vs. PDT alone (*n* = 68) | Photofrin® | Mean survival time of 374 days for PDT vs. 520 for PDT+CT (*p* = 0.021). The 1-year survival rate was significantly higher in the PDT group (88% vs. 58%, *p* = 0.001) Mean OS was 395 days for PDT vs. 566 days for PDT + CT (*p* = 0.09) | No specifics given. | [224] |

| Pancreas | Study Goal | Study Method | PS | Study Outcome | AEs | Reference |
|---|---|---|---|---|---|---|
| Locally advanced unresectable pancreatic adenocarcinoma | First-line treatment | Light dose finding study possibly followed by CT or RT ($n$ = 15) | verteporfin | SD was achieved in 11/13 assessable patients and PD in 2/13, 1 month post-PDT. In 6 patients SD maintained for 3 months. Median OS was 8.8 months | Mild to moderate abdominal pain, mild inflammation | [232] |
| **Bladder** | **Study Goal** | **Study Method** | **PS** | **Study Outcome** | **AEs** | **Reference** |
| Intermediate or high-risk urothelial cell carcinoma | Postoperative PDT | Surgery followed by PDT ($n$ = 17) | HAL | Post-PDT CR rate was 52.9%, 23.5% and 11.8% after 6, 9 and 21 months respectively | Mild or severe irritative bladder/urgency syndrome, urinary tract infections | [235] |
| Recurrent, high grade nonmusclar invasive bladder cancer | Postoperative PDT | Surgery followed by PDT ($n$ = 35) | Radachlorin® | Average follow up was 26.74 ± 6.34 months. The recurrence free rate was 90.9% at 12 months, 64.4% at 24 months and 60.1% at 30 months | No severe adverse effects was detected after PDT treatment | [234] |
| **Female Reproductive Tract** | **Study Goal** | **Study Method** | **PS** | **Study Outcome** | **AEs** | **Reference** |
| Cervical intraepithelial neoplasia 1–3 | Fluorescence diagnosis | Dose-finding study ($n$ = 24) fluorescence only | HAL | Fluorescence intensity increased over time with higher values for 10 mM dose than 4 mM, CIN more fluorescent than normal epithelium | | [242] |
| Cervical intraepithelial neoplasia, human papillomavirus infection | First-line treatment | Topical application of PS and illumination 3–5 h later | HAL | 15/24 patients had complete response; remission rates of 71, 50 and 71% for CIN 1, 2 and 3 | No systemic adverse effects, no cutaneous toxicity. Some patients reported cervical tenderness during illumination | [243] |
| Cervical intraepithelial neoplasia 2 and 3, with human papillomavirus infection | First-line treatment | PDT repeated with 1 week interval | ALA | CIN2 with complete response for 9 months, one CIN3 remained positive for 6 months after 4 treatments | Burning sensation and increased vaginal discharge | [238] |
| Cervical intraepithelial neoplasia 2 and 3 | First-line treatment | Standalone treatment | Photolon® (chlorin e6 derivative) | 104 of 112 (CIN2: 24, CIN3: 88) women had complete response | Pain during treatment, increased body temperature, several patients with mild arterial hypertension after PDT | [239] |
| Cervical intraepithelial neoplasia 1–3 | First-line treatment | Double-blinded dose finding study | HAL or MAL | From initial CIN1 ($n$ = 3), CIN2 ($n$ = 9), CIN3 ($n$ = 13), 9 patients had a complete response, 7 had a partial response 6 months after PDT. No macroscopic changes of the cervix observed | No systemic effects were observed | [247] |

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| Cervical intraepithelial neoplasia 1–3 | First-line treatment | Light- and drug-dose ranging study ($n$ = 67) | MAL or HAL | A 3 h DLI had the best results with CR rates of 50% for MAL (1.2 M), 33% for HAL (10 mM) and 46% for HAL (40 mM). HAL40 with 25 J/cm2 light achieved 29% CR compared to 33% with 50 J/cm2. HAL40 with 3 h DLI followed by a light dose of 50–100 J/cm$^2$ was most effective | cervical pain and spasms and cervical or vaginal discharge | [244] |
| Cervical intraepithelial neoplasia 1 | First-line treatment | PDT vs. Placebo or follow-up only ($n$ = 70) | HAL | HAL: CR of 57% ($n$ = 47) Placebo or follow-up only: CR of 25% ($n$ = 23) ($p$ = 0.04) | Mild to moderate local pain, cramping and vaginal discharge | [245] |
| Cervical intraepithelial neoplasia 1–2 | First-line treatment | Dose-finding study ($n$ = 262) | HAL | No significant difference in response between CIN1/2 patients receiving PDT or placebo. For CIN2 patients alone, only HAL 5% had a statistically significant efficacy compared to placebo with CR in 18/19 ($p$ = 0.009) after 3 months and 18/19 ($p$ = 0.021) after 6 months. HPV clearance was not significantly higher | Pelvic pain, vulvovaginal discomfort, vulvovaginal burning sensation, vulvovaginal pain, genital discomfort, abdominal pain, upper abdominal pain, procedural pain, and postprocedural discomfort | [246] |
| Peritoneal Carcinmatosis and sarcomatosis | Phase II study | 2.5 mg/kg, 48 h drug-light, debulking surgery, intraoperative ill ($n$ = 100 patients) | Photofrin® | No sign. CR or long-term tumor control | Capillary leak syndrome, 2 postoperative deads, 1 intra-abdominal bleeding, 4 adult respiratory distress syndrome, 4 bowel fistulae or anastomica leak, 2 wound dehiscence or delayed wound healing, 2 wound infections, 3 prolonged ileus or small bowel obstruction, reversible abnormal liver function, hypocalcemia and hypomagnesemia, 20 mild photosensitivity | [237] |
| Premalignant lesions of vulva and vagina | Retrospective study | Colposcopy and or vulvoscopy, surface PDT 2 mg/kg, 48 h drug-light, 150 J·cm$^{-2}$ ($n$ = 15 patients) 1 year FU | Photogem® | 3 months FU: 80% (12/15) CR, 1-year FU: 71.4% (10/14) CR | 13.3 % (2/15) Facial edema and urticaria 1/15 perineal pain | [241] |

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| Vulvar HSIL (formally denoted vulvar intraepithelial neoplasia) | Retrospective study | Evaluation of 3 treatment modalities: CO2 laser vaporation, PDT, excision/ vulvectomy ($n$ = 93) Mean FU 53.7 months | ALA | Recurrences CO2: 40.4% PDT: 48.1% Excision: 42% | | [240] |
| **Prostate** | **Study Goal** | **Study Method** | **PS** | **Study Outcome** | **AEs** | **Reference** |
| Early diagnosed prostate cancer | First-line treatment | Dose-finding study and PDT ($n$ = 6) | mTHPC | 67% decrease in prostate specific antigen (PSA) level, Oedema and patchy necrosis shown in MRI scans | No specifics given | [250] |
| Localised prostate cancer | Pre-operative PDT | PDT followed by surgery ($n$ = 19) | 5-ALA | Selectively accumulation of 5-ALA in cancer cells, No PpIX enrichment in benign tissue, stroma (0/19) | Cutaneous phototoxicity | [249] |
| Recurrent prostate cancer | Salvage treatment | VTP after failure of external beam radiation therapy ($n$ = 24) | Tookad® | Regions of Avasculrity with no viable tumor observed in MRI images at 7 days but outside this zone, viable tumor was remained, in all patients In 4 patients, PSA decreased to negligible level | Self-limited hypotension after drug infusion | [251] |
| Recurrent prostate cancer | Salvage treatment | VTP after failure of external beam radiation therapy ($n$ = 28) | Tookad® | 8/16 patients treated with high light dose at least 23 J/cm$^2$ in 90% of prostate volume were biopsy negative at 6 months. PSA level decreased to negligible level in this group of 8 patients | Initial deterioration in voiding fuction which was controllable, rectourethral fistulae in 2 patients | [252] |
| Localised prostate cancer | First-line treatment | Dose-finding study and VTP ($n$ = 84) | Tookad® | At 6 months, 74% of patients were biopsy negative biopsy, Mean percentage of prostate necrosis at 7 days after VTP was 78% | No specifics given | [253] |

| Brain | Study Goal | Study Method | PS | Study Outcome | AEs | Reference |
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| Malignant glioma | FGR | FGR (*n* = 139) vs. conventional surgery (*n* = 131) | ALA | Contrast-enhancing tumor completely ressected in 90% of 139 patients, compared to 47% in 131 patients; 6 months extended progression free survival with FGR | Most frequent early AE: hemiparesis (4 vs. 2); aphasia (3 vs. 0); convulsions (3 vs. 1); and epidural haematoma (1 vs. 1) | [255] |
| Malignant gliomas, metastatic brain tumors, meningiomas | Newly diagnosed or recurrent tumor (not in randomized trial) | PDT (*n* = 112) post-resection | Photofrin® | Overall survival 42 weeks (*n* = 96) | 3 deaths post-PDT; 7 patients increased neurological defect, 2 recovered within 1 month; 4 patients deep vein thrombosis; 75% no complications | [258] |
| Malignant brain tumors | FGR followed by intra-operative PDT | FGR + PDT vs. control | Foscan® | Tumor prediction with 90.7% accuracy; 75% radical resection with FGR, compared to 52% without FGR; mean survival of 9 months for FGR+PDT, compared to 3.5 months | 2 severe toxic responses to sunlight; 1 transitional brain swelling | [259] |
| Malignant glioma | PPIX selectivity (FGR) and bleaching (PDT) | FGR vs. surgery; followed by PDT | ALA | Mean PpIX fluorescence 100-fold increased in viable tumor; PpIX bleached 8, 16 and 1% with 100, 150 and 200 J/cm2, respectively; Complete resection in 65% patients with FGR, compared to 36% | | [256] |
| Glioblastoma multiforme | FGR and repetitive PDT | FGR after surgery and 5 illumination sessions for PDT (*n* = 13) vs. surgery alone (*n* = 14) | ALA, Photofrin® | Mean survival 52.8 weeks compared to 24.6 weeks; mean time to tumor progession 8.6 months, compared to 4.8 months | 3 incidents of deep venous thrombosis, 2 in the study group; no other AE described | [257] |
| Unresectable gliomas | Intraoperative treatment | Intraoperative PDT often followed by CRT (*n* = 14) | talaporfin (NPe6) | Newly diagnosed gliomas: CR 1/6, PR 2/6, DP 1/6, not evaluable 1/6. Median OS was 26 months. Recurrent gliomas: CR 1/8, PR 1/8, SD 2/8, PD 4/8. Median OS was 9 months. All patients had (second) recurrence | Hemiparesis and brain oedema but neither directly PDT related | [260] |
| Primary malignant parenchymal brain tumors | Intraoperative treatment | Multimodal. Surgery and PDT (*n* = 22) | talaporfin (NPe6) | All gliomas: median PFS of 20 months, median LPFS of 22.5 months and a median OS of 27.9 months. Newly diagnosed giomas: median PFS of 12 months, median local PFS of 20 months and OS was 24.8 months | Mild rash, blister, redness of the skin | [261] |

| Other Organs | Study Goal | Study Method | PS | Study Outcome | AEs | Reference |
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| Gastric cancer | Case report | 1 patient inoperable gastric cancer, PDT over 2 years, once with Photofrin®, three times with talaporfin sodium | Photofrin® or talaporfin sodium | Repeated PDT treatments lets patient digest food in natural way | Transient examples of slight anemia and hypoalbuminemia, Photofrin®: slight tanning, slight abdominal pain and diarrhea | [263] |
| AIN grade IIII | Prospective intervention study | PDT 0.075–0.15 mg/kg, 48 h drug-light, red or green light (*n* = 15 patients and 25 PDT sessions) | mTHPC | 28% (7/25) initial CR, 16% (4/25) initial PR, 8 months FU: 7/11 recurrences, Green PDT: 6–15 months FU: 16% (4/25) | Intensive pain, bloody and purulent rectal discharge. anal stricture formation in one patient | [264] |
| AIN III, AIN I or II, Paget's disease | Retrospective study | Photofrin®: 1.2 mg/kg 630 nm light 100 J·cm$^{-2}$ 400 mW cm-2, ALA: 37.5 J·cm$^{-2}$, 2 cycles 3–5 minutes dark interval (*n* = 15 and 26 PDT sessions) Median FU 19 months | ALA and Photofrin® | ALA: 13 patients<br>Photofrin® 1 patient<br>Both: 1 patient<br>10 patients result: 6 initial CR with AIN II or III, with 3 recurrences at 7, 8 and 22 months 3 PR, resolution of symptoms in 4 patients | 1 patient reported significant discomfort | [265] |
| Circumscribed choroidal hemangioma | Prospective, multicenter, nonrandomized, clinical trial | 6 mg m$^{-2}$, 689 nm, 15 min drug-light, 50 J·cm$^{-2}$, 83 s, 1–4 treatments 12 weeks apart FU > 12 months | verteporfin | 69% Visual recovery, Visual acuity increased, Cystoid macular edema regressed, exudative macular detachment disappeared in all but 2, CCH thickness decreased from 3 to 1.7 mm | No severe adverse effect | [266] |
| Amelanotic choroidal melanoma | Curative study | Repeated PDT till flat or no change, 4–16 mm diameter and 1.3–5.7 mm thick lesions, (*n* = 9 patients, 1 with pigmented portion) | verteporfin | 8 apparent CR in 1–14 months, 1 pigmented area remained 2 mm thick, 8 no recurrence FU 34–81 months, 2 local recurrences at 21 and 34 months | No adverse effects | [267] |
| Choroidal metastasis | Retrospective interventional case series | 6 mg m-2, 689 nm, 600 mW cm$^{-2}$ 83 s, 7 mm diameter and 2.9 mm thick lesions, (*n* = 9 CM in 8 eyes) 1 or 2 sessions | verteporfin | 2 non responders, 7 complete control with resolution of subretinal fluid and thickness reduction of 39%, 7 improvement or stabilization of vision | 1 intraretinal hemorrhage | [268] |

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| Circumscribed choroidal hemangioma | Prospective consecutive 2 centered, noncomparative interventional case series | 6 mg m-2, 689 nm, 50 J·cm$^{-2}$ or 100 J·cm$^{-2}$, 83 s, retreatments in case of persistent exudation, ($n$ = 25 subjects) FU > 5 years | verteporfin | 22 patients had 1 PDT session to 100 J·cm$^{-2}$ and no recurrences, 3 PDT sessions to 50 J·cm$^{-2}$ followed by one session to 100 J·cm$^{-2}$, Foveal center thickness decreased from 386.2 to 179.2 μm, Visual acuity improved by 18.5 letters and more than 2 lines in 19 eyes, all showed complete resolution of macular exudation | No treatment-related adverse events or complications identified | [269] |