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Research review

Photodynamic diagnosis for detection of peritoneal carcinomatosis

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ABSTRACT

Background: Peritoneal carcinomatosis is the dissemination of cancer in the peritoneal cavity secondary to abdominal or extra-abdominal malignancies. Accurate assessment of the disease's burden is a challenge because of the complexity of the peritoneal cavity and the small size of the metastatic nodules. Photodynamic diagnosis (PDD) is an emerging technology in tumor diagnosis. A photosensitizer is administered, which is preferentially taken up by cancer cells. The photosensitizer emits fluorescence when exposed to a light of a specific wavelength. This helps distinguish cancer from normal tissues.

Methods: We systematically reviewed the evidence for using PDD in detecting peritoneal carcinomatosis in both animal and human literature. Both Medline and EMBASE databases were searched (November 2014). The titles and the abstracts of all retrieved citations were inspected, and the full articles of the relevant articles were obtained.

Results: A total of 12 human and 18 animal studies were included. Clinical studies have shown PDD to be a safe modality with no significant adverse effects. It increases the detection of malignant peritoneal nodules by 21%–34% in comparison with white light alone. The sensitivity and specificity of PDD were reported at 83%–100% and 95%–100%, respectively. These findings were supported by multiple animal studies, which have shown an increase in the sensitivity of tumor detection when using PDD (72%–91%) in comparison with white light alone (39%).

Conclusions: PDD is a promising modality, which improves the detection of peritoneal carcinomatosis lesions. Further research, however, should investigate the impact of PDD on the patients' therapeutic management and final outcomes.

1. Introduction

Peritoneal carcinomatosis is the dissemination of cancer deposits in the peritoneal cavity. These are most commonly secondary metastases from colorectal, ovarian, urogenital, gastric, and pancreatic cancers, or less frequently metastases from melanomas [1] or malignancies of distant organs such as the breast. Rarely, tumor nodules originate from the

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peritoneum itself (e.g., peritoneal mesothelioma and primary peritoneal carcinoma) [2].

Current therapies for peritoneal carcinomatosis include cytoreductive surgery, which aims to resect all macroscopic disease, combined with heated intraperitoneal chemotherapy (HIPEC) [3,4]. If cytoreductive surgery is not possible, palliative approaches aim to provide symptomatic relief [3]. Despite therapeutic interventions, peritoneal carcinomatosis has a very poor prognosis with median survival of only 8, 7–19, and 22–64 mo for peritoneal carcinomatosis secondary to gastric [5], colorectal [6,7], and ovarian [8] malignancies, respectively.

In the absence of distant metastases, rigorous staging of the peritoneal disease is needed to determine patients' suitability for cytoreductive surgery. Preoperative staging modalities, including computed tomography (CT), magnetic resonance imaging, and positron emission tomography-CT, have a limited ability to detect small (<7 mm) peritoneal nodules [9]. Consequently, diagnostic laparoscopy or laparotomy is used to confirm the diagnosis, provide biopsies for histologic tests, and assess the disease's burden and the appropriateness of cytoreductive surgery [10–13]. However, the complex anatomy of the peritoneum and the small size of some malignant nodules compromise laparoscopic staging accuracy [14]. Laparoscopic staging is even more challenging in second-look procedures where peritoneal carcinomatosis nodules can be confused with granulomas and scar tissue [14].

Photodynamic diagnosis (PDD) is an emerging technology for the diagnosis of cancer. A photosensitizer is administered that preferentially accumulates in malignant tissue and fluoresces when irradiated with a light of a specific wavelength. This enables cancer to be distinguished from normal tissue. PDD is currently used as a diagnostic tool to aid the resection of bladder and brain tumors [15–17]. Preliminary evidence suggests that PDD used during staging laparoscopy and/or laparotomy for peritoneal carcinomatosis might improve the ability to detect small cancer nodules and give a more reliable assessment of the disease burden. This provides an important platform which helps decision-making with regards to patient's management.

This article is the first attempt to systematically review all existing literature from human and animal studies, which investigated the use of PDD for peritoneal carcinomatosis. Considering the limited human evidence, we included animal studies to create an overview of what has been published and how, including judgment on possible animal to human translation. It was thought that this will provide more robust platform to help direct future research and improve the safety of human participants.

2. Methods

2.1. Criteria for study inclusion

2.1.1. Studies

All original peer-reviewed comparative and noncomparative studies of any type were included. Conference proceedings were excluded.

2.1.2. Participants

Patients or animal models with peritoneal carcinomatosis of any origin. The peritoneum of the animal was seeded with cancerous cells to allow growth of tumor nodules inside the peritoneum. Successful achievement of peritoneal carcinomatosis was judged by having more than one intraperitoneal nodule (dissemination model). Animal models where only one solid mass was obtained or seeding was performed outside the peritoneal cavity (e.g., flanks) were excluded.

2.1.3. Interventions

All studies that used any type of PDD as a diagnostic tool to detect malignant nodules within the peritoneum.

2.2. Primary outcomes

- Diagnostic test evaluation: this includes sensitivity, specificity, and positive and negative predictive values.
- Fluorescence to white light detection: this outcome looks into the number of nodules detected under fluorescence light in comparison with the number detected under conventional white light.
- Adverse effects.

2.3. Secondary outcomes

- Tumor to normal (T/N) fluorescence intensity ratio: this outcome looks into the intensity of fluorescence emitted by the tumor lesions and compares it with the fluorescence produced by the surrounding normal tissue. It represents the contrast, which allows the differentiation between tumor and normal tissue.
- Smallest size lesion: this is the smallest size cancer lesion that was detected by fluorescence.

2.4. Search strategy

Literature searches were performed on both MEDLINE (January 1946 to November 2014) and EMBASE (January 1947 to November 2014) databases, to identify both animal and human studies investigating the use of PDD in peritoneal carcinomatosis of any origin. Search terms included "photodiagnosis" or "fluorescen*" or "photodetection" or "photodynamic diagnosis" and "peritone*," in any field. The search was restricted to English written articles.

2.5. Study selection

The selection process was divided into two phases. In the first phase, the titles and abstracts of all citations located through the electronic search were scanned to identify the "relevant articles." The full texts of the "relevant articles" were then obtained and assessed for inclusion and/or exclusion against the eligibility criteria (second phase). The selection process was performed independently by two authors (M.Q.A. and G.G.). In cases of disagreement, a consensual decision was made after discussion of the full article. The references of the "relevant articles" were checked for any additional articles.