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Intraoperative Imaging in Ovarian Cancer: Fact or Fiction?

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Abstract

Tumor-targeted fluorescence imaging for cancer diagnosis and treatment is an evolving field of research that is on the verge of clinical implementation. As each tumor has its unique biologic profile, selection of the most promising targets is essential. In this review, we focus on target finding in ovarian cancer, a disease in which fluorescence imaging may be of value in both adequate staging and in improving cytoreductive efforts, and as such may have a beneficial effect on prognosis. Thus far, tumor-targeted imaging for ovarian cancer has been applied only in animal models. For clinical implementation, the five most prominent targets were identified: folate receptor α , vascular endothelial growth factor, epidermal growth factor receptor, chemokine receptor 4, and matrix metalloproteinase. These targets were selected based on expression rates in ovarian cancer, availability of an antibody or substrate aimed at the target approved by the Food and Drug Administration, and the likelihood of translation to human use. The purpose of this review is to present requirements for intraoperative imaging and to discuss possible tumor-specific targets for ovarian cancer, prioritizing for targets with substrates ready for introduction into the clinic.

THE DETECTION AND MANAGEMENT OF CANCER have benefited greatly from the development of sensitive imaging modalities. Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and ultrasonography all have unique advantages in visualizing tumors, and technical improvements such as multimodality systems (PET-CT, PET-MRI) have led to increasing efficiency and sensitivity and detailed two- and three-dimensional images. However, these modalities are not suitable for real-time feedback during surgery. In diseases with a peritoneal spreading pattern, such as ovarian cancer, cytoreduction is of eminent importance. Intraoperative fluorescence imaging aiding the surgeon in detection of (metastatic) tumor deposits may improve resection rates and thus positively influence prognosis. As tumor-targeted fluorescence imaging is on the verge of clinical implementation, we set out to provide an overview of useful imaging targets in ovarian cancer. In this review, the possible targets for intraoperative imaging in ovarian cancer are evaluated. First, we illustrate the importance of improved tumor visualization during ovarian cancer surgery and describe the basics of fluorescence imaging. Subsequently, the development of tumor-specific tracers for ovarian cancer toward clinical introduction is discussed.

Methods

PubMed was used as the primary database for search queries. The general search method was based on the full name and abbreviation for each target discussed and on combinations of the following search terms: gynecologic cancer, ovarian cancer or carcinoma, intraoperative imaging, and fluorescence imaging. To maximize the search results, we did not prioritize for the presence of the search terms in titles, abstracts, or key words. Relevant articles were selected and examined, including a screening identifying possibly relevant cited reports. Only articles written in English were considered for citation in this review. There was no limitation on the publication date, but emphasis was put on articles published in the last decade.

Imaging in Ovarian Cancer

Ovarian cancer, of which epithelial ovarian cancer (EOC) is the predominant histology, is a major cause of mortality in women, ranking the fifth most common cause of death from cancer.¹ Because of late onset of symptoms, 75% of women are diagnosed with advanced disease, and 5-year survival rates for stage IV cancer are only about 30%.² In advanced disease, the degree of cytoreduction is one of the most important prognostic factors.^{3–5} Given the improved survival associated with complete resection of all visible disease,^{6,7} debate is ongoing as to whether this is a more appropriate definition for optimal cytoreduction than the current standard of residual disease < 1 cm.^{8,9} The size of residual disease after cytoreduction is also of importance for penetration of adjuvant systemic or intraperitoneal chemotherapy into tumor nodules,^{10–13} highlighting the importance of a thorough inspection of the abdomen for metastases.

Preoperative imaging offers a guideline for the multidisciplinary team and in particular the surgeon. However, the accuracy of computed tomography (CT) for adequate staging is around 75%^{14–16} and depending solely on CT may thus result in over- or undertreatment. In discriminating benign from malignant masses, PET-CT is superior to other modalities, with an accuracy rate of 92%, compared to 75% and 83% for MRI and ultrasonography, respectively.¹⁶ For detection of large peritoneal metastases, CT and MRI are equally sensitive, up to 100%.¹⁷ Adding diffusion-weighted MRI to conventional MRI improves the detection sensitivity of peritoneal metastases.^{18,19} The greatest difficulty is the detection of very small tumor deposits in peritoneal carcinomatosis, which are missed by the above-mentioned modalities in 20 to 30% of cases but are pivotal for accurate staging.²⁰ Laparoscopic staging is an attractive, less invasive option for staging and is considered safe in early-stage ovarian cancer.²¹ In more advanced stages, however, adhesions may impede thorough inspection of all abdominal quadrants.²² Therefore, current guidelines recommend exploratory laparotomy as the only fully reliable staging method.^{23,24} As an adjunct to this, intraoperative optical imaging for in vivo tumor detection could be of value for improving both adequate staging and cytoreduction. Real-time fluorescence imaging provides high sensitivity and resolution, illustrated by preclinical studies that report detection resolutions of 0.3 mm in an ovarian cancer xenograft model in mice.²⁵

In Vivo Fluorescence Imaging

Intraoperative imaging is successful only if the tumor-specific signal derived from the targeted optical contrast agent is clearly discernible from the background, leading to low false-negative and false-positive rates of detection. As all tissues have some degree of autofluorescence, the signal from the fluorescent agent is impeded to some extent, especially in visible light wavelengths (400–750 nm). In this respect, the use of near-infrared (NIR) fluorescent dyes (750–1,000 nm) is advantageous for in vivo imaging because surrounding tissues generally absorb little of the emitted signal and light in the NIR spectrum does not

compete with fluorescence in the visible light spectrum.²⁶ Moreover, near-infrared fluorescence (NIRF) has reduced scattering properties compared to fluorescence detection in the visible light spectrum. NIRF imaging therefore gives a high signal at the target site, whereas surrounding tissues emit little to no signal. As this so-called high signal to background ratio is preferable, development of imaging agents is centered on the NIR wavelengths.²⁷ The spectrum of fluorescent agents in the NIR range is broad, but only one has been approved by the Food and Drug Administration (FDA) for human use: indocyanine green (emission \approx 820 nm).^{28,29} Although fluorescein (emission \approx 518 nm) is also FDA approved,³⁰ the emission wavelength of this agent is not within the range of the NIR spectrum. New promising dyes, such as infrared dye 800CW (emission \approx 805 nm), are currently in preclinical testing for toxicity.³¹

With regard to the detection device, emitted NIRF signals cannot be perceived with the naked eye. Therefore, a sensitive multispectral NIR camera system is needed to simultaneously detect the fluorescence and the color signal and process it into one image. The ideal intraoperative camera system is light, portable, and easily operated with high data processing speed and detailed imaging properties. To date, only a few clinically approved intraoperative camera systems and laparoscopic fluorescence cameras have been described. These workable fluorescence camera systems have been extensively described.^{32–35}

Tumor-Specific Targets for Fluorescence Imaging

The ideal marker for tumor-targeted intraoperative NIRF imaging is tumor specific, clinically approved, safe, and nontoxic. Also, the marker needs to be easily conjugated to a NIRF dye.³⁶ In the following paragraphs, we elaborate on five targets that are promising candidates for tumor-specific fluorescence imaging in ovarian cancer. This review is limited to agents that are already FDA approved for therapeutic or diagnostic imaging purposes, thus facilitating introduction into the clinic within the next 5 years.

Folate Receptor

The folate receptor (FR) is one of the most promising targets in EOC. The transmembrane receptor consists of four isoforms, of which FR- α is present on malignant cells, whereas FR- β is located on activated macrophages.³⁷ FR- γ and FR- δ are reported to play a role in regulatory T cells.³⁸ In general, FR- α is overexpressed by approximately 40% of human cancers, but expression rates vary greatly between tumor types.³⁹ Given that FR- α is overexpressed in EOC in 72 to 97%, in both primary tumor tissue and metastatic tumor deposits,^{40,41} applications targeting FR- α can be applied in a large group of patients without prior screening for expression of the target. The advantages of folate as a biomarker are that it binds to FR with high affinity, is inexpensive, can be easily coupled to other substances, and has little or no toxicity.⁴²

Folate and folate conjugates are quickly internalized in the cell via receptor-mediated endocytosis within 2 hours.⁴³ The macromolecule inside the endosome remains intact and can therefore fully exert its function inside the cell.^{43,44} This led to the development of a broad variety of folate-targeted conjugates such as chemotherapeutic agents and radioactive tracers.^{44–48} Studies with ¹¹¹In-DTPA-folate as an imaging agent clearly show uptake in ovarian cancer, as well as in the kidneys, where FR- α is expressed on cells in the proximal tubule under physiologic conditions.^{49,50} Subsequently, a ^{99m}Tc-based folate tracer, EC20, was developed by Endocyte Inc. (West Lafayette, IN). This tracer is cleared more rapidly from the body.^{51,52}

Farletuzumab (MORAb-003) is an antibody with high affinity for FR- α that has been evaluated preclinically and is currently being introduced in the clinic for therapeutic

purposes.⁵³⁻⁵⁵ Furthermore, an imaging study using radiolabeled ¹¹¹In-DOTA-MORAb-003 reports excellent biodistribution and tumor visualization, in both mice and patients.⁵⁶

In short, FR- α is a promising target in EOC, and the above-mentioned FR- α -targeted agents provide sensitive visualization of tumor tissue. This leads us to believe that folate conjugated to a fluorescent dye could be suitable for intraoperative imaging in FR- α -expressing tumors, a concept that has already been reported in a preclinical study in mice.⁵⁷

Hypoxia-Related Proteins

Hypoxia plays an important role in the development and aggressiveness of several types of solid tumors, including EOC.⁵⁸ Tumors develop hypoxic areas when blood supply becomes inadequate in rapidly proliferating tissue. Moreover, hypoxic tumors show more aggressive behavior and appear to have a worse prognosis owing to a greater potential to metastasize, a decreased response to cell damage owing to inactivation of the tumor suppressor gene *P53*, and increased resistance to both radio- and chemotherapy.⁵⁹⁻⁶¹ In instances of low oxygen pressure, hypoxia-inducible-factor 1 (HIF-1) is expressed, of which the alpha subunit (HIF-1 α) affects several regulatory processes, such as apoptosis and proliferation, through modulation of more than 100 hypoxia-related genes and their hypoxia-responsive elements (HREs).⁶²⁻⁶⁵ Two of these are of special significance in the context of intraoperative imaging in EOC. Both epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor 1 (VEGFR-1) are upregulated by HIF-1 α in EOC^{66,67} and could be suitable targets for imaging applications for two reasons. First, given that most ovarian cancers are diagnosed in a late stage, when the tumor is already of reasonable size, it is realistic to assume that there are areas of hypoxia and thus involvement of hypoxia-inducible genes. This is confirmed by genomic and proteomic testing of patient material.⁶⁸⁻⁷⁰ Second, hypoxic tumors tend to metastasize more rapidly, and the associated hypoxia-inducible genes can be detected in the primary tumor as well as in metastatic tumor deposits.⁷¹ This implies that their protein products or, even at the cellular level, their HREs may serve as a target in intraoperative imaging to visualize both the primary tumor and foci of disseminated disease.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF), an important regulator of angiogenesis and vascular permeability, is involved in various steps of normal ovarian function as well as carcinogenesis.^{62,72,73} VEGF-related growth factors and receptors form primary signaling pathways in tumor angiogenesis and have been implicated as regulators of angiogenesis and disease progression in EOC through proliferation, cell survival, and metastasis.^{73,74} Triggering this so-called “angiogenic switch” by overexpression of a potent angiogenic growth factor is an important step in the growth and dissemination of EOC. VEGF activates two high-affinity transmembrane tyrosine kinase cell surface receptors, VEGFR-1 and VEGFR-2, which stimulate intracellular signaling cascades, leading to endothelial cell recruitment, activation, proliferation, and survival, as well as increasing vascular permeability.⁶² Of all VEGF subtypes, the VEGF-A ligand and VEGFR-2 receptor seem to play a particularly prominent role in EOC.⁷⁵

Several studies are now focused on the value of VEGF inhibition in the treatment of EOC.⁷⁶ Apart from therapeutic relevance, some of these agents could also be used for tumor-targeted imaging. In this light, we focus on bevacizumab (Avastin, F. Hoffmann-La Roche Ltd, Basel, Switzerland), a promising drug that has already been useful in several conventional imaging applications, such as PET. Bevacizumab is a humanized monoclonal antibody that binds to and neutralizes VEGF-A, preventing its association with endothelial

receptors and, as a consequence, inhibiting angiogenesis. Inhibiting microvascular outgrowth is believed to slow down the growth of all tumor tissue, including metastatic sites. Recent clinical trials have reported that bevacizumab prolongs progression-free survival in EOC.⁷⁷⁻⁸⁰

Bevacizumab itself can be conjugated to radioactive substances for application in PET. This was illustrated in a murine ovarian tumor xenograft model, in which bevacizumab conjugated to ¹¹¹In or ⁸⁹Zr showed clear tumor uptake on microPET.⁸¹ Subsequently, ¹¹¹In-bevacizumab SPECT can clearly visualize tumor lesions in melanoma patients.⁸² These developments suggest that bevacizumab may also be conjugated to NIRF dyes and as such provide a fluorescent agent for intraoperative imaging of tumor activity.

Apart from targeting VEGF-A, fluorescence imaging of the VEGFR has also been shown, using a single-chain fusion protein (scVEGF) coupled to the fluorescent dye Cy5.5.⁸³

Although VEGF-guided imaging seems promising, its specificity could be limited by the fact that VEGF is also scavenged in fluids and thus ascites and serves as an important survival factor for healthy cells experiencing chemical or physical stress.⁸⁴⁻⁸⁸ Possibly, the presence of VEGF-A in ascites might hamper the detection of tumor spots in vivo. However, considering the high expression of VEGF in tumor tissue, the signal to background ratio may be sufficient to distinguish the strong tumor-related signal from the much weaker signal from healthy tissues. This assumption was illustrated in the above-mentioned murine model with radiolabeled bevacizumab,⁸¹ although it should be taken into account that the murine peritoneum does not excrete human VEGF-A. Moreover, during cytoreduction, the abdomen is thoroughly inspected, consecutively focusing on specific regions of interest—that is, the abdomen, pelvis, diaphragm, and liver capsule—and VEGF expression in other tissues will probably not interfere with imaging of this specific region. Furthermore, ascites can be drained during surgery for improving detection.

Epidermal Growth Factor Receptor

Members of the epidermal growth factor family and the associated receptor, EGFR, play a significant role in ovarian cancer as the majority of EOCs express high levels of EGFR.⁸⁹⁻⁹¹ This overexpression of EGFR is an independent factor for poor outcome and low survival rates.⁹²⁻⁹⁴ The EGFR superfamily is made up of four distinct but structurally similar tyrosine kinase receptors. Upregulation leads to cell proliferation, differentiation, migration, adhesion, protection from apoptosis, and transformation.⁹⁵

A few EGFR-targeted monoclonal antibodies are already available in the clinical setting, including cetuximab and panitumumab.⁹⁶ These are used in therapeutic regimens but may also prove useful for imaging purposes. Panitumumab, either radiolabeled or in its pure form, conjugated to indocyanine green, has been shown to yield excellent optical imaging signals when used in a mouse model.^{97,98} Radiolabeled cetuximab for tumor-targeted imaging has also been successfully used in murine tumor models.^{99,100} To date, no clinical studies have been performed using an EGFR antibody for this type of tumor-targeted imaging. However, the existence of FDA-approved antibodies and promising preclinical data may lead to rapid translation into the clinic.

Because EGFR is expressed not only by cancer cells but also by healthy cells, one might suggest that tumor-specific imaging using EGFR as a target is impossible. However, expression rates in tumor tissue are 20 to 50 times higher than in the surrounding healthy tissue.¹⁰¹ This makes the signal to background ratio large enough for sensitive tumor-targeted imaging. As such, EGFR can also be regarded as a potential target for intraoperative imaging in ovarian cancer.

Chemokine Receptor 4 and Chemokine Ligand 12

Dissemination of disease in EOC starts with the loss of cell adhesion molecules and degradation of the extracellular matrix, after which migration of tumor cells commences.¹⁰² In this process, there is a key role for matrix metalloproteinases (MMPs) and several chemokine-receptor pairs, of which chemokine receptor 4 (CXCR4) and its chemokine, chemokine ligand 12 (CXCL12), or stromal cell-derived factor 1 (SDF-1) are among the most well studied.¹⁰³ Many of the mechanisms governing the structure and migration of cells are influenced and disrupted by hypoxia and HIF-1 (for a comprehensive review, see Gort and colleagues¹⁰²). Although not specific for ovarian cancer, both MMP and CXCR4-CXCL12 indicate areas of disseminated disease and are therefore worth exploring as possible targets for intraoperative imaging.

Several chemokine-receptor pairs are expressed in tumors cells, as well as by the surrounding stroma.^{103,104} The CXCR4-CXCL12 axis supports chemotaxis of tumor cells to the metastatic site and subsequent hatching and proliferation. In ovarian cancer, the CXCR4-CXCL12 pathway seems to have a more prominent role than other chemokine-receptor pairs and portends a worse prognosis.¹⁰⁵⁻¹⁰⁸ CXCR4 and CXCL12 staining was demonstrated in 59% and 91% of ovarian tumor cells, respectively, whereas no expression was seen in healthy tissue.¹⁰⁹ On binding to CXCR4, CXCL12 is internalized and the receptor is recycled to the cell surface, where it is ready for further action within 15 minutes.¹⁰⁷ Overexpression of CXCL12 was found in ascites, inducing the migration of tumor cells and contributing to peritoneal dissemination.^{109,110}

Visualization of CXCR4 on the cell membrane was shown in vitro by using a CXCR4-directed fluorophore.¹¹¹ For in vivo targeting, both the receptor and the chemokine can be targeted by a monoclonal antibody, which in itself can be conjugated to an imaging agent. In a mouse model, a CXCR4-radiolabeled antibody was successfully used for tumor visualization in SPECT-CT.¹¹² For PET, the CXCR4 antagonist ADM3100 conjugated to ^{99m}Tc proved useful in locating tumor xenografts in mice.¹¹³

Matrix Metalloproteinases

MMPs degrade several components of the extracellular matrix and are associated with tumor progression and metastasis. Several subtypes, among which are MMP1, MMP2, MMP7, and MMP9, are overexpressed in EOC.¹¹⁴⁻¹¹⁹ CXCL12 is known to activate MMP2 and MMP9 in ovarian cancer, further contributing to the dissemination of tumor cells.¹²⁰

A few preclinical studies have been conducted on NIRF imaging of MMP activity in cancer, using so-called “smart activatable probes” that are activated by MMPs.¹²¹⁻¹²³ Although these probes are not yet suitable for human use, they could play an important role in the future development of ovarian cancer targeting.

These results indicate that substantial progress is being made in visualization of MMP and CXCR4 activation and expression in EOC. These factors could possibly find their way to the clinic as targets for tumor-specific imaging in ovarian cancer.

Discussion

The greatest potential of intraoperative fluorescence imaging in EOC lies in improved detection of metastatic tumor deposits, leading to more complete cytoreduction. Additionally, intraoperative fluorescence imaging may be valuable in other gynecologic malignancies and in a broader range of oncologic diseases. As many tumor types express the biomarkers mentioned in this review, albeit to different degrees, these tumor-targeted contrast agents could potentially be applied in a broad spectrum of diseases. Overexpression

of FR- α is seen in 40% of human cancers, including breast, lung, renal, and brain cancer³⁷; however, there is great variation in expression patterns between tumor types.³⁹ Hypoxia has been shown to occur in several types of solid tumors, including gynecologic cancers such as cervical¹²⁴ and endometrial¹²⁵ carcinoma, and is in the vast majority of cases correlated with worse survival rates. HIF-1 α , VEGF, and EGFR are all overexpressed in endometrial cancer.¹²⁵ Furthermore, treatment with cetuximab has been shown to inhibit tumor growth and peritoneal dissemination in a mouse model for endometrial cancer.^{125,126} These findings suggest that contrast agents targeting hypoxia-induced gene products such as VEGF and EGFR could also be of value in the surgical treatment of endometrial cancer with peritoneal dissemination. In cervical cancer, peritoneal dissemination is rare, limiting the application of tumor-targeted contrast agents for the purposes of cytoreductive surgery. However, these agents may be successful in identifying parametrial disease, especially in the laparoscopic setting, as MRI and CT perform poorly in staging of advanced disease, with sensitivity rates of 53% and 42%, respectively.¹²⁷

Although the concept of intraoperative tumor-targeted imaging is promising, more research is needed to define the value of each independent target. In the development of possible tumor-targeted agents, specificity and sensitivity of the agent for its target are of the utmost importance. The variable expression of biomarkers, not only between tumor types but also within a solid tumor, may call for a combination of tumor-targeted agents to obtain high sensitivity rates. In addition, fluorescent agents with varying wavelengths could be used to localize various active biomarkers using multispectral fluorescence imaging. Conversely, a panel of agents with the same wavelength may provide the most comprehensive image of tumor activity.

Apart from evaluating the value of each independent tumor-targeted contrast agent, attention needs to be focused on development of commercially available user-friendly and safe intraoperative camera systems and laparoscopic fluorescence cameras.

Conclusion

Treatment of advanced EOC primarily consists of surgical cytoreduction followed by chemotherapy. As the extent of cytoreduction greatly influences prognosis, detailed detection and resection of metastatic and residual tumor tissue during surgery are a necessary prerequisite to improve patient survival. New techniques such as intraoperative optical imaging using highly specific tumor-targeted fluorescent optical agents combined with sophisticated camera systems can help improve cytoreductive efforts. Preclinical and translational studies will determine the efficacy of such an approach in the near future.

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