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Fluorescent imaging of cancerous tissues for targeted surgery ☆

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ABSTRACT

To maximize tumor excision and minimize collateral damage are the primary goals of cancer surgery. Emerging molecular imaging techniques have made "image-guided surgery" developed into "molecular imaging-guided surgery", which is termed as "targeted surgery" in this review. Consequently, the precision of surgery can be advanced from tissue-scale to molecule-scale, enabling "targeted surgery" to be a component of "targeted therapy". Evidence from numerous experimental and clinical studies has demonstrated significant benefits of fluorescent imaging in targeted surgery with preoperative molecular diagnostic screening. Fluorescent imaging can help to improve intraoperative staging and enable more radical cytoreduction, detect obscure tumor lesions in special organs, highlight tumor margins, better map lymph node metastases, and identify important normal structures intraoperatively. Though limited tissue penetration of fluorescent imaging and tumor heterogeneity are two major hurdles for current targeted surgery, multimodality imaging and multiplex imaging may provide potential solutions to overcome these issues, respectively. Moreover, though many fluorescent imaging techniques and probes have been investigated, targeted surgery remains at a proof-of-principle stage. The impact of fluorescent imaging on cancer surgery will likely be realized through persistent interdisciplinary amalgamation of research in diverse fields.

Contents

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1. Introduction: the concept of targeted surgery

Tremendous advancement in molecular biology research has revolutionized clinical oncology practice and has led to the emergence of "*targeted therapy*" in the last century. Targeted therapy of cancer is a new type of regimen that involves the use of drugs or other modalities to precisely identify and eradicate cancer cells and tissues while generally causing minimal damage to normal cells and tissues. Through extensive preclinical research, targeted therapy has begun to be translated into certain clinical practices including medical, radiation and surgical oncology [1].

In medical oncology, targeted therapy can be termed as "molecular targeted therapy" and refers to development and application of a class of medications that block the growth and spread of cancer by interrupting the specific molecular abnormalities that drive growth and progression [2]. Traditional chemotherapy kills both normal and malignant dividing cells by interrupting essential cellular events, such as DNA replication and microtubule assembly. Molecular targeted therapy focuses on molecular abnormalities that are specific to cancer cells, such as aberrant proteins or receptors expressed solely or dominantly in cancerous tissues [3]. Therefore, this strategy offers higher response rates with fewer adverse effects when compared with conventional chemotherapy. The target of molecular targeted therapy is a cancer biomarker, and the impetus for driving the progress of the technique is our burgeoning understanding of the molecular biology of cancers.

In radiation oncology, targeted therapy can be termed as "targeted radio therapy" and refers to radiating cancerous tissues or organs more precisely, which allows for higher radiation dose delivery with less toxicity. Intensity-modulated radiation therapy and image-guided radiation therapy are two such targeted radiotherapy strategies, and they allow further dose escalation and a reduction in normal tissue radiation exposure [4,5]. Moreover, therapeutic radiation on the molecular scale has further expanded the application of targeted radiotherapy through delivering radioactivity specifically to cancer cells by targeting cancer biomarkers, molecular pathways, or gene expression [6–9]. Similarly, the targets of targeted radiotherapy are either tumor foci or specific molecular or genetic characteristics of cancer, and the impetus for driving the field forward is an improvement in imaging and radiation technology.

However, in surgical oncology, the concept of targeted therapy remains ambiguous and largely undefined. What does targeted surgery mean? For solid tumors in particular, it can simply imply a surgery with a definite target. In the target-specific context, surgeons can work towards their ultimate goals of maximizing tumor excision, minimizing collateral damage, and minimizing the risk of metastasis or recurrence. Therefore, the following two issues are essential for targeted surgery: (1) how to define the target (tumor) and from what aspects will a surgeon evaluate the target; and (2) what strategies can be taken to realize the process of a targeted cancer tissue resection. To address both issues, one indispensable approach is the use of non-invasive imaging techniques.

Current imaging modalities such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) may facilitate the accurate diagnosis, staging and visualization of tumors (target), which are prerequisites for successful surgical therapy. Furthermore, advances in optical fluorescence imaging (FI), which uses fluorochromes to enhance the visualization capability of the operating surgeon beyond that of white-light reflectance, provides a major opportunity to improve surgical outcomes. Subsequently, "image-guided surgery" has been increasingly adopted, which involves the use of imaging as surgical navigation to visualize the tumor intra-operatively and allows the surgeon to maximize tumor excision and minimize collateral damage at the tissue-scale [10]. With the explosion of molecular imaging, "molecular diagnostic screening" and "molecular image-guided surgery" using targeted molecular probes are emerging and have the potential to improve the visualization, characterization, and measurement of biological processes at the molecular and cellular levels for surgery [11]. These advances have expanded the current concept of surgery and hold significant promise to improve surgical precision from tissue-scale to molecule-scale. Therefore, the term "targeted surgery" will be used in this paper to indicate surgical approaches that are assisted by molecular imaging.

"Targeted surgery" can be defined as the precise, specific and radical resection of cancerous tissue according to histologic characteristics or even molecular signatures that are acquired by radiology and/or molecular imaging. This method results in high resectability rates with little damage to normal tissues and better outcome, under the precondition of ensuring minimal metastatic potential. The critical part of the definition is to match a surgical approach with the biology of the tumor. Therefore, the target of targeted surgery is cancerous tissue, and the impetus for driving progress of the technique is molecular imaging that promotes surgical precision from tissue-scale to molecule-scale. Targeted surgery includes, but is not limited to, image-guided surgery, and it emphasizes the assessment of the molecular characteristic of cancerous tissue beyond morphological changes and/or discoloration. Furthermore, surgeons use imaging techniques both during operation and also before and after surgery coordinately. Unlike "minivasive surgery", such as endoscopic, laparoscopic and robotic technologies, which has a goal of minimizing collateral damage, targeted surgery stresses maximum tumor excision while minimizing the potential for metastasis and recurrence in terms of tumor biology through either open-field surgery or minivasive surgery. In the era of targeted surgery, we must understand that the goal is not the simple safe excision but more importantly an understanding of how and if surgery will alter a tumor's inherent biology in vivo.

A variety of non-invasive molecular imaging modalities can be used in targeted surgery. Optical imaging using near-infrared (NIR) fluorescence light is an emerging non-invasive in vivo cancer imaging modality, and it is an ideal methodology for targeted surgery. In this review we first offer a framework for conceptualizing targeted surgery. Next, we provide a summary of target-specific fluorescence imaging probes, which serve as the key components that accelerate the development of fluorescent imaging for targeted surgery. Then, we give an overview of the current status in fluorescent imaging of cancerous tissues for targeted surgery in order to identify advantages and limitations. Special emphasis will be placed on discussing the obstacles that impede the future development of fluorescent imaging in targeted surgery and offering potential solutions. Finally, the concept of "system molecular imaging" will be defined in this review. While fluorescent imaging techniques have been widely explored in preclinical research, targeted surgery remains in the stage of proof-of-principle for clinical research. Optimizing the impact of fluorescent imaging for cancer patient is expected to be realized through the persistent interdisciplinary amalgamation of research in diverse fields.

2. Fluorescent imaging for targeted surgery

2.1. Inherent characteristics enable fluorescent imaging suitable for targeted surgery

Molecular imaging techniques serve as the most important prerequisite for targeted surgery. Until now, many different non-invasive molecular imaging modalities have been used in targeted surgery, either with or without combination with a navigation system. Those that could provide intraoperative guidance for the tumor resection, mainly including MRI [12,13], US [14], and FI were of special focus. Each of these modalities has its own merits and limitations in visualizing tumors for targeted surgery, as reviewed previously [11]. Among them, FI is the most suitable for targeted surgery because of its inherent properties and advantages: (1) no ionizing radiation is required;(2) high-resolution images are produced at a high speed; (3) the readout of fluorescence imaging is in real time, making it the optimal choice for intraoperative