EUROPEAN UROLOGY 65 (2014) 947–964

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Endo-urology

Editorial by M. Pilar Laguna on pp. 965–966 of this issue

Current Perspectives in the Use of Molecular Imaging To Target Surgical Treatments for Genitourinary Cancers

Francesco Greco [a,*], *Jeffrey A. Cadeddu* [b], *Inderbir S. Gill* [c], *Jihad H. Kaouk* [d], *Mesut Remzi* [e], *R. Houston Thompson* [f], *Fijs W.B. van Leeuwen* [g], *Henk G. van der Poel* [h], *Paolo Fornara* [a], *Jens Rassweiler* [i]

[a] *Department of Urology and Renal Transplantation, Martin-Luther University, Halle an der Saale, Germany;* [b] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [c] *USC Institute of Urology, Catherine and Joseph Aresty Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA;* [d] *Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH, USA;* [e] *Department of Urology, Landesklinikum Korneuburg, Korneuburg, Austria;* [f] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [g] *Department of Radiology, Interventional Molecular Imaging Laboratory, Leiden University Medical Center, Leiden, The Netherlands;* [h] *Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [i] *Department of Urology, SLK Kliniken Heilbronn, University of Heidelberg, Heilbronn, Germany*

Article info

Article history:
Accepted July 17, 2013
Published online ahead of print on August 7, 2013

Keywords:
Molecular imaging
Genitourinary oncologic surgery
Surgical navigation
Image-guided surgery
Augmented reality

Abstract

Context: Molecular imaging (MI) entails the visualisation, characterisation, and measurement of biologic processes at the molecular and cellular levels in humans and other living systems. Translating this technology to interventions in real-time enables interventional MI/image-guided surgery, for example, by providing better detection of tumours and their dimensions.
Objective: To summarise and critically analyse the available evidence on image-guided surgery for genitourinary (GU) oncologic diseases.
Evidence acquisition: A comprehensive literature review was performed using PubMed and the Thomson Reuters Web of Science. In the free-text protocol, the following terms were applied: *molecular imaging, genitourinary oncologic surgery, surgical navigation, image-guided surgery*, and *augmented reality*. Review articles, editorials, commentaries, and letters to the editor were included if deemed to contain relevant information. We selected 79 articles according to the search strategy based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria and the IDEAL method.
Evidence synthesis: MI techniques included optical imaging and fluorescent techniques, the augmented reality (AR) navigation system, magnetic resonance imaging spectroscopy, positron emission tomography, and single-photon emission computed tomography. Experimental studies on the AR navigation system were restricted to the detection and therapy of adrenal and renal malignancies and in the relatively infrequent cases of prostate cancer, whereas fluorescence techniques and optical imaging presented a wide application of intraoperative GU oncologic surgery. In most cases, image-guided surgery was shown to improve the surgical resectability of tumours.
Conclusions: Based on the evidence to date, image-guided surgery has promise in the near future for multiple GU malignancies. Further optimisation of targeted imaging agents, along with the integration of imaging modalities, is necessary to further enhance intraoperative GU oncologic surgery.

* Corresponding author. Department of Urology and Kidney Transplantation, Martin-Luther-University, Ernst-Grube-Strasse 40, 06120 Halle an der Saale, Germany.
E-mail address: francesco.greco@uk-halle.de (F. Greco).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2013.07.033

1. Introduction

In recent decades, imaging technologies have realized significant developments, resulting in their current important role in clinical oncology [1]. The field has expanded greatly and now comprises various modalities including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) [2–4]. Because each modality has its specific advantages and disadvantages, combining different techniques (eg, PET and CT) has become the practice for tumour detection, staging, and treatment evaluation [1–5]. However, when surgery is required, translation of these molecular images to the operative field remains a challenging obstacle.

Recently, advances in molecular imaging (MI) technology enable the noninvasive imaging of specific molecular pathways that are fundamentally involved in disease processes [6–8].Various hallmarks of cancer can be used to detect malignant cells or tissues such as growth factor signalling receptors, limitless replicative potential, sustained angiogenesis, and increased proteolytic activity resulting in tissue invasion and metastasis [9,10]. MI evaluates the molecular signature and changes in cellular physiology and function rather than anatomy. These molecular pathways are likely to be expressed earlier than anatomic deformation, allowing more sensitive representations of the disease process. In addition, detecting tumours via their unique molecular signatures may help to significantly improve the specificity of diagnoses. Ideally this information is put in the hands of the surgeon in real-time to warrant image-guided surgery.

This review summarises and critically analyses the currently available evidence of intraoperative navigation and imaged-guided surgery for genitourinary (GU) oncologic surgery.

2. Evidence acquisition

A comprehensive literature review was performed using PubMed and Thomson Reuters Web of Science between April 1995 and April 2013. Using free-text protocol, the following terms were applied: *molecular imaging, genitourinary oncologic surgery, surgical navigation, image-guided surgery*, and *augmented reality*. Review articles, editorials, commentaries, and letters to the editor were included only if deemed to contain relevant information. Cited references from the selected articles and from review articles retrieved in the search were also assessed for significant manuscripts not previously included. Studies published only as an abstract or presented without an abstract, and reports from meetings and studies not published in English were not included in the review.

We selected 79 articles according to the search strategy based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria [11] (Fig. 1; Table 1).

To describe and assess the development of each surgical innovation and at the same time to clearly depict the stages of the research, all included studies were also segmented into sequential stages according to the IDEAL methodology (I = idea, D = development, E = exploration, A = assessment, L = long-term study) [12].

3. Evidence synthesis

3.1. Quality of the studies and level of evidence

According to the IDEAL methodology [12], 15 studies represented stage 0 [1,7,8,16,17,19,30,35,36,48–50,62,68,72], 11 studies were classified as stage 1 [23,25,28,31,32,51,54,57–60], 18 studies as stage 2a [24,26,27,37,41,43,45,52,61,63–65,67,70,81,83,84], 20 studies as stage 2b [2,3,5,6,9,10,15,22,33,34,44,46,47,66,69,71,78–80], 11 studies as stage 3 [4,18,20,29,38–40,42,53,55,75], and 5 studies were considered stage 4 [21,73,74,76,77].

We defined clinical studies included in the analysis according to the levels of evidence defined by the Oxford Centre for Evidence-based Medicine (http://www.cebm.net). There was one study with level of evidence (LE) 1a [82], 21 studies with LE 1b [17,23,25,33,35,39,42,46,48,49,52,53,60,61,63,64,75–79], 26 studies with LE 2a [1–7,9,10,15,16,18–22,24,29,30,35,43–45,71,73,74], 19 studies with LE 2b [8,26–28,32,36,41,51,54,55,57–59,62,67–69,72,80], 10 studies with LE 3b [37,38,40,47,50,65,66,70,81,83], and 2 studies with LE 4 [31,84].

3.2. Interventional molecular imaging

3.2.1. Definition

A number of definitions have been proposed for MI. In 2005, an MI summit, sponsored by the Radiological Society of North America and the Society of Nuclear Medicine and Molecular Imaging (SNM), recommended the following definition: "Molecular imaging techniques directly or indirectly monitor and record the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications" [13].

In 2007, the SNM Molecular Imaging Centre of Excellence recommended an expanded definition, whereby MI represents the visualisation, characterisation, and measurement of biologic processes at the molecular and cellular levels in humans and other living systems. MI typically consists of two-dimensional (2D) or three-dimensional (3D) imaging as well as quantification over time.

The techniques used to enable an interventional MI/image-guided surgery include optical imaging and fluorescent techniques, an augmented reality (AR) navigation system, MRI spectroscopy, PET, and SPECT [14]. Interventional MI has the potential to personalise patient care because it can reveal the clinical biology of the patient and of the tumour [6].

3.2.2. Techniques and new developments

Major strides in our understanding of the molecular biology of GU malignancies have led to the development of novel techniques in biomedical imaging [15]. In GU oncologic surgery, intraoperative assessment of the tumour-free margin is critical for the prognosis of the patient. Currently,