REVIEW ARTICLE

How to objectively evaluate the impact of image-guided surgery technologies

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Abstract

Purpose This manuscript aims to provide a better understanding of methods and techniques with which one can better quantify the impact of image-guided surgical technologies.

Methods A literature review was conducted with regard to economic and technical methods of medical device evaluation in various countries. Attention was focused on applications related to image-guided interventions that have enabled procedures to be performed in a minimally invasive manner, produced superior clinical outcomes, or have become standard of care.

Results The review provides examples of successful implementations and adoption of image-guided surgical techniques, mostly in the field of neurosurgery. Failures as well as newly developed technologies still undergoing cost-efficacy analysis are discussed.

Conclusion The field of image-guided surgery has evolved from solely using preoperative images to utilizing highly specific tools and software to provide more information to the interventionalist in real time. While deformations in soft tissue often preclude the use of such instruments outside of neurosurgery, recent developments in optical and radioactive guidance have enabled surgeons to better account for organ motion and provide feedback to the surgeon as tissue is cut. These technologies are currently undergoing value assessments in many countries and hold promise to improve outcomes for patients, surgeons, care teams, payors, and society in general.

Keywords Image-guided surgery · Value · Evaluation

Introduction

All surgeons depend on preoperative imaging for surgical planning. Image-guided surgery takes many different forms and has been defined as any intervention that is assisted by pre- or intraoperative imaging [1]. Shortly after Roentgen's publication on X-rays in 1895, interventionists began planning procedures guided by the images—The first surgeries described involved removing foreign bodies such as bullets [2], which provided value when these objects could not be located by palpation alone. The development of new medical technologies has a demonstrated history of innovators applying their discoveries in a variety of diagnostic and therapeutic areas to both test clinical utility and share their results. X-ray equipment was cheap, easy to use, and

revolutionary in that it was the first modality that allowed one to see through the body. However, the true cost of these image-guided diagnoses and interventions came with the discovery of adverse events produced by high amounts of radiation exposure [3].

From the early 1900s until the advent of tomographic reconstruction methods, X-ray guidance demonstrated value in orthopedic and neurologic surgical procedures for two reasons: the high contrast provided by the bone and the importance of better understanding of vasculature in the brain. The use of plates and screws as fixation devices for fractures increased after the introduction of the X-ray, as the images were used to guide the intervention [4]. Due to limitations in size and tube power, early systems had difficulty imaging anything but the extremities and until ventriculography [5] and angiography [6] were described, brain tissue provided poor contrast. The first thalamotomy was performed using ventriculography—a procedure that would not have been possible without image guidance [7]. The discussion surrounding the new imaging modality seldom involved cost,

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as the X-ray machines were cheap and ubiquitous. While advances such as image intensifiers and flat panel detectors have vastly improved image quality, the principles of fluoroscopy remain the same as first described toward the end of the nineteenth century.

In the modern context, image-guided surgery can be thought of in terms of a procedure guided by preoperative (ultrasound, CT, MRI, PET, SPECT), in vivo optical (fluorescent, fluorescence lifetime, Raman, multispectral, photoacoustic), and other in vivo methods (intraoperative ultrasound, radio-guided techniques). Many systems rely upon imaging devices present in hospitals as standard of care diagnostic machines and necessitate additional equipment in terms of fixtures or software for operation. Image guidance helps with surgical planning, can assist surgeons with situational awareness, and has helped facilitate the development of minimally invasive procedures.

Methods of technology evaluation

When thinking about objective evaluation of the impact of new medical technologies, nearly every discussion in the modern era centers around cost-effectiveness. Traditional value in healthcare has been defined as outcomes achieved per dollar spent [8, 9]. The framework proposed by Berwick and later expanded on by Sikka et al. is often cited, as the goals of all involved should be taken into account: In addition to patient outcomes, the provider, payor, policy makers, and care team should be considered when discussing technology adoption [10, 11]. An outcome should not simply be thought of as negative margin in oncology—it has been described in terms of restoring the patient's ability to above or near where they were prior to the disease, comfort in lessening the burden of the illness, and calm in the sense of reducing angst surrounding treatment [12]. Societal impacts can be more subjective, as a younger woman requiring treatment for a gynecologic issue might still be in the workforce as compared to an older man requiring a prostate intervention who may be retired. Most would agree that a therapy allowing the woman to return to work more quickly would benefit society. However, the older man may have other duties, such as being a caregiver to a partner.

Determining the cost-effectiveness of new medical technologies is confusing and has been a topic of debate for many decades. Combined with the fact that medical resource allocation is determined by a mix of federal/state governments, insurance companies, physicians, and patients, there is often no single solution to the question of cost-efficacy. Economic evaluation is a key component to any healthcare system, as the merit of one therapy must be weighed by the resources used in what are typically resource-constrained environments. In the mid-1990s, Australia began requiring

the inclusion of economic analyses with the application for pharmaceutical approvals. The National Institute for Health and Care Excellence (NICE) in the UK followed suit, requiring such data for both pharmaceuticals and other technologies. This gave rise to the health technology assessment (HTA), which traditionally tends to have higher importance in single-payer systems [13]. HTAs are non-binding recommendations, and the impact of such assessments on reimbursement decisions in many countries is unclear. However, the UK, Australia, France, Poland, and Romania have been vocal about the key role that HTAs play in decision-making. It is important to note that HTAs can be performed by insurance groups, health organizations, and academic research institutions. While industry stakeholders are often asked to participate in HTAs, they do not perform the assessment themselves. Fontrier et al. provide an excellent overview of the differences in how efficacy assessments are made and implemented in a variety of countries [14].

Opportunity costs are typically determined and compared with diagnostic or therapeutic benefit. Cost-efficacy or utility analyses are performed, with traditional assessment of the value of technologies and pharmaceuticals in healthcare relying heavily upon the incremental cost-effectiveness ratio (ICER) or quality-adjusted life year (QALY) [15]. The quality-adjusted life year is an equation used to estimate how much a treatment will add to the duration of a patient's life and increase his/her quality of life over those years. A year of perfect health is a QALY of 1, while a year of less than perfect health is assigned a QALY of between 0 and 1. The ICER is related and is equal to the ratio of the added cost of the intervention divided by the gain in effectiveness of the treatment. $ICER = \frac{\Delta Cost}{\Delta Effectiveness}$. Different healthcare systems determine what ICER or cost per QALY gained they are comfortable with per procedure [16]. While frameworks are well-developed for pharmaceuticals, assessment of the value of devices, which are often required for image-guided surgery, tend to be more nuanced. As opposed to pharmaceuticals, device designs can change quickly with different user groups implementing the device in different ways, and the cost of the device used might be a small percentage of the larger surgical cost for implantation. Nonetheless, the UK, Japan, and France now implement a variety of techniques to assess medical device efficacy, although it is not known how individual hospitals take such assessments into account [17]. Hyeraci provides a nice explanation of value-based pricing using ICER methodology for 48 different medical devices with data from the Italian market. With a willingness to pay threshold of €60,000 per QALY, they found a majority of medical devices to be cost-effective but stated that publication bias might have had an influence on this finding, [18] as economic analyses reporting positive results are more likely to be published than those reporting negative results.

Physicians serve an important role in both inventing and identifying new technologies that can enhance patient care. A clinician's ability to change practice to adapt to new devices relies upon access to information relating to the clinical value and profitability of the new tools [19]. One study found that physician preference items accounted for upwards of 60% of hospital supply spending and hospitals routinely strategize how to reduce such costs [20]. Technology adoption committees have been employed within healthcare entities to allow these discussions to occur [21]. Such committees must take the practicing physician's preference into account and come up with their own pros and cons when it comes down to the impact of the medical device on their operating budget. As consolidation within the healthcare industry continues, decisions for medical device purchase may become more centralized, relying upon HTA-like assessments for adoption.

Image guidance technologies

An overview of technologies used in image guidance is provided by Peters [22]. One of the first interventions enabled by image guidance was biopsy, a crucial part of assessing patient health and guiding appropriate therapy. On the diagnostic front, as half of the cost of breast cancer management involved getting a definitive diagnosis, image-guided biopsy reduced the need for invasive surgical excision, subsequently reducing the cost of diagnosis by upwards of 50% [23] and has become standard in the modern era with core biopsies helping to guide the necessity or extent of nodal dissection. Already an established technique for most tumor types, the need for tissue samples in the era of personalized medicine will change the way that the cost-effectiveness of biopsy is assessed, as knowing the molecular signature of tissues will be increasingly important in helping to guide highly specific and sometimes expensive treatment.

Shortly after the development of PET, CT, and MRI, a journal dedicated to image-guided surgery was started, recognizing the need to communicate among researchers [24] and contained many articles related to "computer-assisted surgery," the predecessor to "image-guided surgery." Due to difficulties in visualizing the instrument tip in neurosurgery, computers were used to assist in trajectory guidance [25, 26]. As computational power allowed for better visualization and reconstruction of 2D planar images into 3D models [27, 28], attempts to use these modalities to guide surgical approaches and interventions increased. Stereotactic frames such as those described by Spiegel [29] enabled procedures to be performed by the interventionist using the imaging device's coordinate system [30], and device holders were utilized to more easily move along defined trajectories [31]. Performance of these procedures was not widespread due to difficulties encountered in implementation and clinical workflow.

As most early imaging techniques were focused on the brain, early image-guided surgical exploration mostly involved stereotactic guidance for neurosurgical procedures [32–36]. As the brain and spine typically undergo only rigid body transformations when a patient is positioned for a procedure, the bulk of image-guided interventions involved these organs. Electromagnetic and optical trackers became part of navigation systems in order to account for rigid body motions and to determine the location of the tip of surgical instruments through the procedure [37–39]. Although the advent of laparoscopic surgery increased the need to improve surgeon situational awareness and compensate for a loss of haptic tissue feedback, efforts to apply image guidance to nonrigid anatomies such as urologic and hepatobiliary applications were not successful mostly due to the large, unpredictable deformations encountered between the preoperative imaging and surgical positioning of the patient [40, 41]. Meanwhile, advances in neuroimaging such as tractography and blood oxygenation level dependence imaging allowed better mapping of regions and created a demand for tools to help with navigation in neurosurgery.

Images were first exported from the imaging devices themselves, and subsequently, systems were developed specifically to import, process, and provide guidance using preoperative images and digitizers in an attempt to provide a better experience for the interventionist and their team. The Brainlab system and the NeuroStation (later renamed StealthStation) were developed and commercialized by Brainlab (Munich, Germany) and Stealth Technologies (acquired by Sofamor Danek, now Medtronic), respectively. Neurosurgeons found these systems to provide improved situational awareness, which is key when trying to co-register a preoperative imaging scan of a lesion to current tool position. Ultimately, improved correlation to the preop image let to more complete resections of tumors, which improved patient survival [42]. While these systems required capital expenditures by hospitals, the comparatively low cost coupled to the benefits of neuronavigation in spinal and cranial procedures led to few formal cost studies.

The placement of pedicle screws, often used in spinal stabilization procedures, was revolutionized with the advent of fluoroscopy and CT. They are sometimes placed incorrectly, or at the wrong level altogether when using X-ray guidance [43]. Several groups have proposed that the use of image guidance systems would reduce the adverse events commonly associated with pedicle screw misplacement, such as poor fusion and nerve damage, both of which can result in a revision surgery. Pedicle perforation rates came down from 13.4% to under 5% through the use of a CT system [44]. Most navigation platforms have demonstrated value in reducing the risk of breach during pedicle screw placement,

where operative time, neurological complications, and blood loss are also key clinical metrics [45]. A retrospective cost-effectiveness study found that the capital equipment required to perform intraoperative CT navigated screw placement was only cost-effective at institutions performing 425 or more cases per year. It is important to note that this single institution study only found a 1% change in misplaced screws when using imaging and navigation [46].

As image guidance became standard for cranial procedures, some began performing interventions in dedicated imaging suites [47] to account for changes in tissue location, including the well-known brain shift that occurs during craniotomy. The cost-effectiveness of an MRI-neuro suite for image-guided surgery provided compelling data in some use cases but failed to catch on commercially [1] partly due to the complexity of maintaining a dedicated MRI, poor image quality, and a lack of MR compatible surgical instruments. Data was presented supporting the use case of MR-guided brain biopsies vs standard frame biopsies, with a single institution study saving between $1000 and $2500 net per procedure after the cost of the imaging system was considered. It was proposed that the estimated $2000 additional procedure cost of the MRI suite would easily be absorbed in procedures costing upwards of $25,000 [48]. This was a very different value proposition than a capital outlay of $30,000 for a stereotactic frame device. While a large system like GE's double donut intraoperative MRI ultimately did not succeed in the marketplace, it demonstrated the importance that a large medical imaging company placed on the field of image-guided surgery and influenced the development of the IMRIS' "MRI on rails" concept as well as smaller, more application-specific systems [49, 50].

As image guidance systems and other medical devices became more and more complex, regulatory bodies noted the importance of proper training and understanding in order to prevent inadvertent misuse and resulting adverse events. After publishing a draft guidance on human factors engineering in 2016, final recommendations for such studies were recently issued by the US Food and Drug Administration [51].

The application of traditional image guidance tools to soft tissue procedures highlighted the need for intraoperative imaging modalities in which relevant information could be co-registered to the white light surgical view. An example is the evolution of lymph node detection in a variety of anatomic sites, and it illustrates how image-guided surgery can positively impact clinical outcomes to provide true value. Lymphedema resulting from axillary node dissection can be a major complication from a quality of life perspective in breast/melanoma procedures, and sentinel lymph node biopsy has almost completely replaced the more invasive technique [52, 53]. Much of this has been enabled by the development of image guidance to localize the sentinel node,

including the use of blue dye and radioisotopes [54, 55]. Image guidance has allowed subsequent studies to determine the importance of the state of the sentinel node in guiding the therapeutic intervention [56–58]. The use of indocyanine green (ICG) changed lymph node visualization significantly, as after the demonstration of the technique in lung [59], breast [60], and gastric cancers [61, 62] with prototype systems, camera manufacturers began to include an excitation source and filter sets for fluorescence excitation of the dye in their systems. Such devices must adhere to the appropriate safety standards (IEC 60601–2-18 and 60,825–1) for endoscopy, which speak to safe power output of optical radiation to avoid tissue damage, for regulatory approval. As opposed to many image guidance technologies in the neurosurgical and orthopedic fields, these systems had simple user interface and were easy for surgeons to use. This, coupled with the fact that the near infrared signal did not obscure the imaging field, was largely responsible for the rapid adoption of the use of ICG over blue dyes for nodal mapping.

A similar case is the use of ICG to help prevent anastomotic leaks in colon cancer surgery—the idea being that the ideal site of anastomosis should be perfused rather than ischemic tissue. Several studies have demonstrated reduced leak rates when ICG is used to select the site for an anastomosis [63–65]. A recent Canadian analysis found the use of ICG to be cost-effective in this application when the probability of leak is above 4.9% [66] and admitted that the sensitivity analysis is highly dependent on whether or not ICG truly makes a difference in leak rate, which is still a debate among colorectal surgeons [67]. It is important to note that the cost of the capital equipment has not been included in such studies, as the option is low-cost or included on most endoscopic systems. In addition, the cost of a dose of ICG itself is quite low, ranging from €8 in Japan to €80 in many European countries.

The ability to visualize the near-infrared signal of ICG on commercial endoscopes demonstrated to several groups the existence of a potential market for fluorescence guided surgery. Imaging dyes that target a number of markers present on various cancers [68–70] as well as structures [71, 72] have been published in the literature, although few have made it to human use. Imaging agents undergo rigorous preclinical safety studies as part of regulatory filings; however as with all pharmaceuticals, there may be undiscovered risks that must be weighed against potential benefits. In addition, unlike radionuclides, where particles can be counted and quantified, current fluorescence imaging systems present data in a more subjective manner, with signal vs background intensity interpretation left up to the user.

Nearly 10 years after clinical demonstration by Stummer [73], Gliolan (5-aminolevulinic acid) was among the first targeted fluorophores approved in the EU (2007), with an indication for high grade glioma. The Phase III trial of

Gliolan demonstrated a higher rate of complete resection and improved 6-month progression free survival [74]—a clear benefit over the white light cohort. Despite subsequent approval in the USA, a decade later, Gliolan has not been a commercial success, with annual revenues of approximately $16M. It is important to note that the cost of Gliolan is absorbed into the diagnosis-related group (DRG) reimbursement payment for tumor removal, which is a frequent occurrence for new technology in the USA, as data is collected regarding real-life efficacy and cost-effectiveness. The use of Gliolan is emblematic of cost-efficacy analysis in the image-guided surgery space—a rudimentary analysis demonstrated that Gliolan is "cost-effective" when the metric of imaging complete resection is used based off of the initial approval data, yet actual patient data from the study was not provided [75]. A separate study in Spain found the compound to be cost-effective, adding €4550 per complete resection achieved over white light alone [76]. While it is generally accepted that a more complete resection results in a better progression-free survival rate, a recent review concluded that the possibility of increased neurologic damage due to an increase in excised tumor tissue over white light remains [77].

van Dam demonstrated in vivo use of a folate—a targeted dye developed by Phil Low at Purdue University [78]. Ten years later, a near-infrared version of the imaging agent received FDA approval for imaging ovarian and subsequently lung cancers. To date, On Target Laboratories has not reported significant revenue from the drug, although the company recently received a new technology add-on payment (NTAP) of up to 65% of the cost of the imaging agent ($4250), effective October 1, 2023. To receive such a payment, the technology must be novel, offer substantial improvement over the standard of care as well as to be inadequately paid for under the existing treatment codes. NTAP payments are good for 3 years, during which time the company can gather data in support of a separate reimbursement code.

Most nuclear medicine–based image-guided surgery techniques have relied upon compounds used in radiology due to availability. Minimally invasive radio-guided thyroidectomy has been shown to have positive benefits in terms of efficacy, length of stay, and costs in hyperparathyroidism—Those patients undergoing traditional neck exploration stayed in the hospital 1.35 days, while a majority of the radioguidance group was discharged the same day [79] in addition to spending less time in the OR as well as the recovery room. A variety of mechanisms have been explored for imaging prostate cancer in part for diagnosis and in part for image-guided therapies, including those designed to image abnormal metabolism, bone metabolism, or prostate cancer-specific receptors present on cells. Li et al. provide a comprehensive review of such agents [80].

Like earlier attempts to justify the costs of diagnostic imaging devices to reduce invasive interventions for patients with metastatic disease who might not benefit from surgery, one of the key benefits of prostate-targeted imaging involves localizing primary or recurrent prostate cancer for therapy management. In most instances, the location of cells leading to biochemical recurrence is unknown, making the ideal salvage therapy modality difficult to determine. Patients might undergo treatments such as surgery, radiotherapy, or androgen deprivation, without truly knowing if the cancer is local or metastatic. Should partial gland focal therapies emerge as a viable treatment option, it is expected that localization of residual disease will become much more important—both from an initial guidance perspective as well as treating local recurrence [81].

There has been excitement in the past decade regarding the development of nuclear medicine agents targeting prostate-specific membrane antigen (PSMA)—a transmembrane protein found in all prostatic tissue that has been found to have increased expression with severity of cancer [82, 83]. The murine anti-PSMA monoclonal antibody 7E11-C5.3 linked to ^{III}indium was first used to image prostate cancer [84] and subsequently developed into the commercial imaging agent [^{111}In]In-capromab pendetide (ProstaScint, Cytogen Corporation, Princeton, NJ), which gained FDA approval in 1996. Despite showing higher sensitivity and specificity than CT or MRI for lymph node staging, the use of the imaging agent to guide therapy remained controversial, and ProstaScint failed in its commercialization attempt, with pricing between $1400 and $2000. Annual revenues never exceeded $15M and were estimated to be less than $1M when Aytu Pharma discontinued the product in 2018 [85]. Certain imaging characteristics such as poor anatomic resolution of SPECT scans, a delay between administration and imaging of approximately 6 days, as well as a 2.5 h scan time might have contributed to poor adoption.

The inherently better resolution of PET imaging has contributed to the recent success of new Ga-68 and 18F PSMA PET imaging agents, which are routinely being used to guide surgical decision-making both in terms of lymph node location and extra capsular extension [86]. Despite improved 5-year survival rates, intraoperative detection of prostate cancer with the goal of negative surgical margins remains elusive, with positive margins occurring in up to 38% of cases [87, 88]. Much like the first decade of computed tomography focused on determining the clinical benefits and efficacy of the technique in different indications, a few studies focused on cost-efficacy. Recent data from Australia concluded that PSMA PET/CT saved between $959 and $1412 per patient when looking for nodal vs metastatic disease as compared with conventional imaging, which consists of an abdominal/pelvic CT plus a bone scan [89]. The cost savings results from improved sensitivity and specificity of the

PSMA technique, leading to the avoidance of local treatment (prostatectomy or radiation therapy) for men with distant metastatic disease. It is important to note that the result was highly dependent on the better sensitivity/specificity of the technique, in addition to the fact that the cost of a PSMA scan in Australia is less than that of conventional imaging. In contrast, studies of PSMA PET in Europe and the USA found significantly increased costs over conventional imaging in countries where the cost of the imaging agent and scan were much higher [90]. Neither study was able to predict the impact that PSMA PET imaging would have on patients from a therapeutic management cost point of view, as the technology is in the early stage of adoption. This is the crux of all issues related to cancer diagnosis and care—can the additional information provided by imaging change the therapeutic management of the patient in a meaningful way that improves outcomes from a survival or quality of life point of view? Can a PSMA PET scan demonstrating metastatic disease stratify patients away from costly therapy such as prostatectomy or radiation that may not improve their chances of survival? The original reimbursement for fludeoxyglucose (FDG) imaging specifically cited PET's ability to stratify patients away from surgical management in 21% of cases with pulmonary nodules, in 35% of those with suspected recurrent colon cancer, and in 36% of patients with metastatic melanoma when compared to CT scanning [91]. The surgeries avoided resulted in a 2:1 cost savings if PET was used as a follow-on imaging procedure yet increased to more than 3:1 in lung cancer and 4:1 in colorectal cancer and melanoma when PET was used as the primary imaging modality. Fludeoxyglucose was subsequently reimbursed in the USA when used for the initial staging of suspected metastatic non-small cell lung cancer or suspected solitary pulmonary nodules to chart the extent of disease and plan for appropriate therapy. Reimbursement for imaging of recurrent colorectal cancer, lymphoma staging, and the detection of recurrent melanoma followed [92].

The conjugation of Tc99 to PSMA ligands has brought about the possibility of intraoperative guidance using external, laparoscopic, and robotically held imaging detectors—it is likely that the use of in vivo detectors coupled with novel image guidance methods will dramatically improve disease detection as it has with other indications such as melanoma [93]. Local detection of PSMA has the potential to detect residual disease with sensitivities and specificities much higher than those achieved with ex vivo imaging modalities due to increased capture of gamma photons and the avoidance of stray data from bladder accumulation of imaging agent. Maurer demonstrated the ability to use ^{111}In-labeled PSMA to detect metastatic lymph nodes in patients [94] as well as a 99Tc version to identify recurrent prostate cancer [95]. It is possible that targeted agents will change the paradigm away from extensive lymph node dissections in favor of targeted, guided excision, leading to quality of life improvements for patients and reduced operating room time. Despite the initial enthusiasm, it is important to understand that the overall effect on clinical decision-making remains to be seen and, as with many developments in the urologic space, may take decades to properly understand. This holds true for fluorescent-linked PSMA markers as well [96, 97], where the hypothesis is that better visualization of disease leads to improved resection, which in turn leads to improved survival. A comprehensive review of PSMA-guided surgery was recently published by Berrens [98].

Conclusion

Image-guided surgery has evolved from using preoperative images to guide interventions to intraoperative, real-time detection of sensitive structures or cancer. The true value of diagnostic radiology in the surgical realm initially was to stratify patients who would not benefit from invasive procedures. Improved patient outcomes were next demonstrated by using preoperative imaging to enable procedures to be performed less invasively, providing improved quality of life to the patient and saving healthcare systems resources. As the intraoperative use of preoperative images failed to catch on for soft tissue procedures, innovations in fluorescent and molecularly guided techniques have recently begun to augment surgeons' senses. Initial data is promising, yet many of the innovations have yet to undergo formal health technology assessments necessary to gain reimbursement from governmental agencies.

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