*review*

# Imaging perfusion changes in oncological clinical applications by hyperspectral imaging: a literature review

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**Background.** Hyperspectral imaging (HSI) is a promising imaging modality that uses visible light to obtain information about blood flow. It has the distinct advantage of being noncontact, nonionizing, and noninvasive without the need for a contrast agent. Among the many applications of HSI in the medical field are the detection of various types of tumors and the evaluation of their blood flow, as well as the healing processes of grafts and wounds. Since tumor perfusion is one of the critical factors in oncology, we assessed the value of HSI in quantifying perfusion changes during interventions in clinical oncology through a systematic review of the literature.

**Materials and methods.** The PubMed and Web of Science electronic databases were searched using the terms "hyperspectral imaging perfusion cancer" and "hyperspectral imaging resection cancer". The inclusion criterion was the use of HSI in clinical oncology, meaning that all animal, phantom, *ex vivo*, experimental, research and development, and purely methodological studies were excluded.

**Results.** Twenty articles met the inclusion criteria. The anatomic locations of the neoplasms in the selected articles were as follows: kidneys (1 article), breasts (2 articles), eye (1 article), brain (4 articles), entire gastrointestinal (GI) tract (1 article), upper GI tract (5 articles), and lower GI tract (6 articles).

**Conclusions.** HSI is a potentially attractive imaging modality for clinical application in oncology, with assessment of mastectomy skin flap perfusion after reconstructive breast surgery and anastomotic perfusion during reconstruction of gastrointenstinal conduit as the most promising at present.

Key words: hyperspectral imaging; oncology; resection; perfusion; cancer

## Introduction

Cancer is the leading health problem in the world. Only in the EU-27 each year are 2.7 million people diagnosed with cancer, while 1.3 million die from the disease.[1] To deal with cancer, knowledge of cancer physiology is essential, where tissue perfusion is one of the most important physiological parameters. Perfusion of tumors is critical in their development and growth. Early studies have shown that tumor growth is dependent on the development of vasculature that has the capacity to supply oxygen and nutrients to dividing tumor cells.[2] However, the vasculature is important not only for the supply of oxygen to tumors but also for the delivery of drugs into tumors.[3] Finally, vasculature is also important for the response of tumors to surgery and other ablative techniques, such as ra-

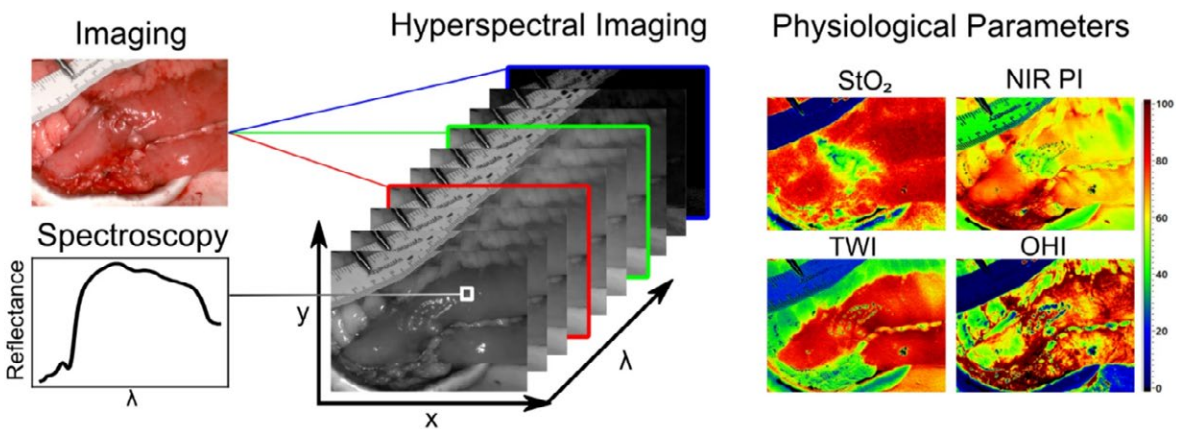


**FIGURE 1.** Structure and composition of hyperspectral images and physiological parameters derived from the images, which are typically displayed in false color.

NIR PI = near-infrared perfusion index; OHI = organ hemoglobin index; $StO_2$ = oxygen saturation of tissue; TWI = tissue water index

Taken from Pfahl *et al.*[15] and reprinted with permission from the publisher.

diotherapy and thermal and nonthermal ablative techniques.[4,5]

It was demonstrated that information about the tumor and healthy tissue perfusion can improve therapy outcome either by guiding tumor resection[6,7] or monitoring the reperfusion of the resected tissues (e.g., anastomosis or tissue flaps).[4,5] Conventional techniques for perfusion imaging in oncology are CT and MR imaging.[10] CT perfusion imaging provides information on tissue hemodynamics by analyzing the first passage of an intravenous contrast bolus through the vessels. On the other hand, MR perfusion imaging utilizes either endogenous or exogenous tracers. In the latter case, it is based on following an injected bolus of contrast agent over time, which is then used to determine the perfusion characteristics of tissues. While both imaging techniques are promising, radiation exposure (CT), potential adverse events due to contrast (CT/MRI), limited access (MRI), high cost (MRI), and inability to scan at the bedside or in operating theater are disadvantages of the conventional techniques.[10] To address these shortcomings, various imaging techniques, including optical imaging, have been explored for tissue perfusion imaging.[11,12] In optical imaging, the optical contrast of tissues is intrinsically sensitive to tissue abnormalities, such as changes in oxygenation, blood concentration or scattering.[13,14] These changes are characteristic of many tumors, since they include angiogenesis, hypervascularization, hypermetabolism, and hypoxia, making optical imaging techniques promising candidates for perfusion imaging in oncology.

Hyperspectral imaging (HSI) is an emerging optical imaging technique that uses light to obtain information about perfusion, or more specifically about oxygenation, water content or hemoglobin content of the tissue. The distinct advantage of HSI is that it is a noncontact, nonionizing, and noninvasive modality and does not require a contrast agent. HSI integrates conventional imaging and spectroscopy techniques by creating a set of images called a hypercube, which contains the spectral signature of the underlying tissue and in turn points to clinically relevant changes, such as angiogenesis or hypermetabolism. Figure 1 illustrates the structure and composition of hyperspectral images and physiological parameters derived from these images.

HSI was originally employed in remote sensing applications[16,17] and then expanded into other fields, such as vegetation type and water source detection[18,19], wood product control[20], drug analysis[21], food quality control[22-25], artwork authenticity and restoration[26,27], and security[28]. HSI is also an attractive modality in the medical field and has been successfully applied for the detection of various types of tumors, particularly in conjunction with histopathologic diagnosis.[29-31] HSI has, *inter alia*, already proven value in plastic and vascular surgery, where assessing perfusion predicted the outcome of healing processes in transplants and wounds.[32,33]

How valuable HSI could be in quantifying perfusion changes during interventions in clinical oncology remains unclear, and to that end, we decided to systematically review the literature with

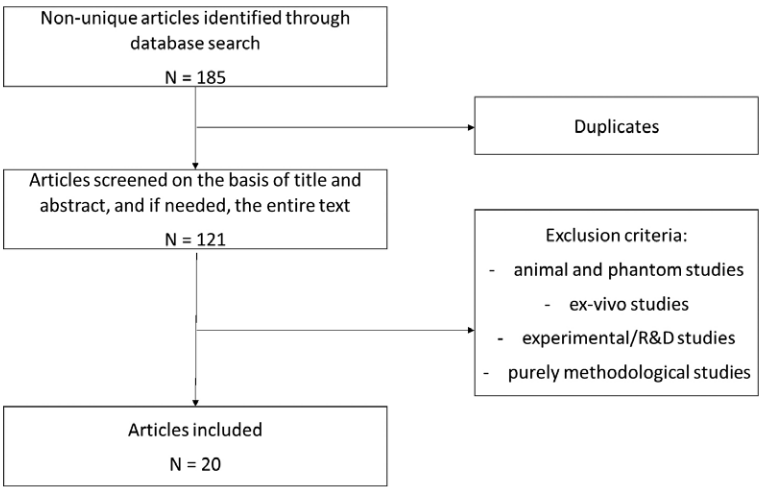


**FIGURE 2.** Flow diagram of the selection strategy.

the intention of exclusively focusing only on studies in which HSI was performed on patients in the clinical oncology setting.

## Materials and methods

Two authors (R.H. and M.M.) conducted jointly – to preclude potential bias – a comprehensive literature search on October 3, 2022 through PubMed and Web of Science electronic databases using the following search terms: »hyperspectral imaging perfusion cancer« and »hyperspectral imaging resection cancer«. No restrictions in publication date or language were imposed. The inclusion criterion was the application of the hyperspectral imaging modality in the oncological clinical setting, meaning that all animal and phantom, *ex vivo*, experimental, research and development, and purely methodological studies were excluded. Special care was taken that duplications were removed, both across databases and across studies; for example, if the study was first published in proceedings and later in the journal, then proceedings article was considered a nonprimary publication and therefore excluded. Studies were categorized with respect to the anatomical location of the tumors.

## Results

A flow diagram of the selection strategy is shown in Figure 2; in total, 101 and 84 articles were found to be of interest in the PubMed and Web of Science databases, respectively. After excluding duplicates and applying the exclusion criteria, first considering the title and abstract, and next, if necessary, reading the entire article, 20 articles were identified for further analysis. The anatomical locations of tumors in the selected articles were as follows: kidneys (1 article), breasts (2 articles), eye (1 article), brain (4 articles), entire gastrointestinal (GI) tract (1 article), upper GI tract (5 articles) and lower GI tract (6 articles).

### Kidneys

Pioneering effort in assessing perfusion by means of HSI in clinical oncology was the work of Best *et al.*[34] They applied modality to monitor renal oxygenation during partial nephrectomy using the parameter called the percentage of oxyhemoglobin ($HbO_2$) and categorized 26 patients into the preoperative groups of high (>75% $HbO_2$) and low (<75% $HbO_2$) oxygenation. Parameter $HbO_2$ has proven useful before, during and after the application of a clamp, with an example of the image presented in Figure 3. The study demonstrated that patients with low oxygenation had a statistically significant postoperative decline in estimated glomerular filtration rate. While further research is needed, HSI indicates potential for assessing susceptibility to renal ischemic injury in patients undergoing partial nephrectomy.

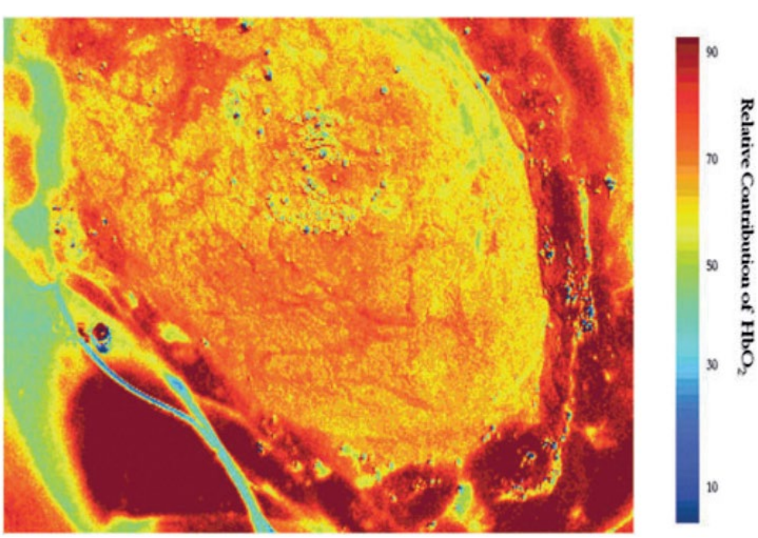


**FIGURE 3.** Images of the kidney depicting the percentage of $HbO_2$ as a function of color. A dark red represents high values while the yellows and greens indicate lower values.

Taken from Best *et al.*[34] and reprinted with permission from the publisher.

**TABLE 1.** Included articles reporting the use of hyperspectral imaging (HSI) to quantify perfusion changes in clinical applications in oncology

| Reference | Year of publication | Number of patients | Oncologic intervention | System | Algorithm |
|---|---|---|---|---|---|
| **Kidneys** | | | | | |
| Best[34] | 2013 | 26 | Partial nephrectomy | DLP HSI, 520–645 nm | Supervised multivariate least squares regression |
| **Eye** | | | | | |
| Rose[35] | 2018 | 8 | Radiation retinopathy | Tunable laser, 520–620 nm with 5 nm steps | PHYSPEC software (Photon etc., Montreal, QC, Canada) |
| **Breasts** | | | | | |
| Chin[36] | 2017 | 43 | Skin response to radiation | OxyVu-2™ (Hypermed, Inc., Waltham, MA), 500–600 nm | The OxyVu-2™ software (Hypermed, Inc., Waltham, MA) |
| Pruimboom[8] | 2022 | 10 | Mastectomy skin flap necrosis | TIVITA™ (Diaspective Vision GmbH, Am Salzhaff, Germany), 500–1000 nm with 5 nm step | TIVITA™ (Diaspective Vision GmbH, Am Salzhaff, Germany) |
| **Brain** | | | | | |
| Fabelo[37] | 2018 | 22 | Craniotomy for resection of intraaxial brain tumor | Hyperspec VNIR A-Series (HeadWall Photonics, Massachusetts, USA), 400–1000 nm | Spectral angle mapper |
| Fabelo[38] | 2018 | 5 | Craniotomy for resection of intraaxial brain tumor; all 5 patients with grade IV glioblastoma | As in Fabelo[37] | As in Fabelo[37] |
| Fabelo[39] | 2019 | 6 | Craniotomy for resection of intra-axial brain tumor; all 6 patients with grade IV glioblastoma | As in Fabelo[37] | As in Fabelo[37] |
| Fabelo[40] | 2019 | 22 | Craniotomy for resection of intraaxial brain tumor | As in Fabelo[37] | As in Fabelo[37] |
| **Entire GI tract** | | | | | |
| Jansen-Winkeln[41] [Article in German] | 2018 | 47 | Gastrointestinal surgery with esophageal, gastric, pancreatic, small bowel or colorectal anastomoses | As in Pruimboom[8] | As in Pruimboom[8] |
| **Upper GI tract** | | | | | |
| Kohler[9] | 2019 | 22 | Hybrid or open esophagectomy followed by reconstruction of gastric conduit | As in Pruimboom[8] | As in Pruimboom[8] |
| Moulla[42] [Article in German] | 2020 | | Video presentation of hybrid esophagectomy | As in Pruimboom[8] | As in Pruimboom[8] |
| Schwandner[43] | 2020 | 4 | Hybrid esophagectomy followed by reconstructing gastric conduit | As in Pruimboom[8] | As in Pruimboom[8] |
| Hennig[44] | 2021 | 13 | Hybrid esophagectomy followed by reconstructing gastric conduit | As in Pruimboom[8] | As in Pruimboom[8] |
| Moulla[45] | 2021 | 20 | Pancreatoduodenectomy | As in Pruimboom[8] | As in Pruimboom[8] |
| **Lower GI tract** | | | | | |
| Jansen-Winkeln[46] | 2019 | 24 | Colorectal resection | As in Pruimboom[8] | As in Pruimboom[8] |
| Jansen-Winkeln[47] | 2020 | 32 | Colorectal resection | As in Pruimboom[8] | As in Pruimboom[8] |
| Pfahl[48] | 2022 | 128 | Colorectal resection | As in Pruimboom[8] | As in Pruimboom[8] |
| Jansen-Winkeln[49] | 2021 | 54 | Colorectal resection | As in Pruimboom[8] | As in Pruimboom[8] |
| Jansen-Winkel[n5]0 | 2022 | 115 | Colorectal resection | As in Pruimboom[8] | As in Pruimboom[8] |
| Barberio[51] | 2022 | 52 | Colorectal resection | As in Pruimboom[8] | As in Pruimboom[8] |

GI = gastrointestinal

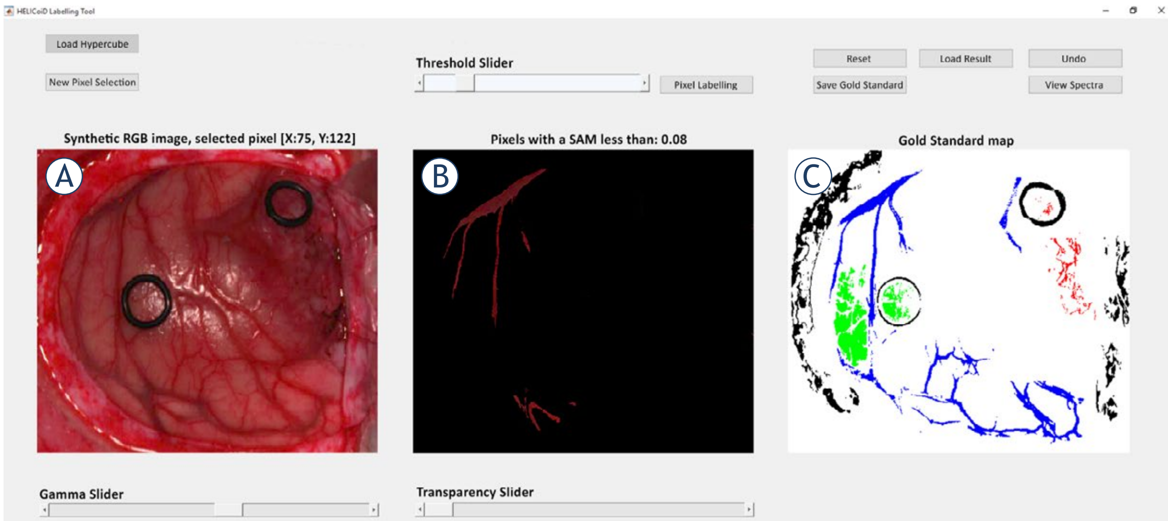


**FIGURE 4. (A)** Red-Green-Blue (RGB) representation of the imaged brain, including normal and tumor tissue. **(B)** Extraction of blood vessels from hyperspectral images using the spectral angle mapper algorithm (SAM). **(C)** Tissue classification map generated from hyperspectral images: tumor tissue is red, normal tissue is green, blood vessels are blue, and background is black.

Taken from Fabelo *et al.*[38] and reprinted with permission from the publisher.

## Eye

In the study of Rose *et al.*[35], clinicians used Doppler spectral domain optical coherence tomography (SD-OCT) in 8 patients diagnosed with radiation retinopathy to measure total retinal blood flow, while retinal blood oxygen saturation was quantified by a specially designed HSI retinal camera. They found that blood flow in the retinopathy eye was significantly lower than that in the fellow eye, while arteriolar oxygen saturation and venular oxygen saturation were higher in the retinopathy eye than in the fellow eye. Unfortunately, researchers conducted no follow-up studies, in which they would further evaluate microvascular changes due to radiation-induced retinopathy.

## Breasts

Chin *et al.*[36] studied a dose–response relationship between radiation exposure and oxygenated hemoglobin in 43 women undergoing breast-conserving therapy radiation. The authors concluded that HSI may prove useful as an objective measure of patients' skin response to radiation dose. However, they also noted that interpatient variability remains a challenge, as approximately 40% of the variability in change in oxygenated hemoglobin is accounted for by dose, 25% by individual woman, and 35% by causes that they could not identify.

Pruimboom *et al.*[8] used HSI in a prospective clinical pilot study enrolling women with breast reconstruction and detected mastectomy skin flap necrosis in 3 out of 10 patients. Somewhat analogously to the study of Best *et al.*[34], they found that tissue oxygenation was statistically significantly lower in the group of patients who developed flap necrosis than in the group of patients who did not. It appears that HSI is specifically suited for the early detection of flap necrosis, which could in turn aid in the timely and accurate debridement of necrotic tissue. Future work should confirm the modality's potential also in identifying partial deep inferior epigastric artery perforator (DIEP) flap necrosis.

## Brain

Fabelo *et al.*[37-40] developed an intraoperative HSI acquisition system and were able to assemble an *in vivo* hyperspectral human brain image database with the overall goal of accurately delineating tumor tissue from normal brain tissue. As the brain tumor typically infiltrates the surrounding tissue, it is extremely difficult to identify the border; in addition, both overresection of adjacent normal brain tissue and leaving tumor tissue behind have detrimental impacts on the results of the surgery and patient outcomes, either adversely affecting the patient's quality of life or causing tumor progression.

The work of Fabelo *et al.* was performed as a part of the European Future and Emerging Technologies (FET) project HELICoiD (HypErspectraL Imaging Cancer Detection).

In their first methodological paper, they designed a special cancer detection algorithm utilizing spatial and spectral features of hyperspectral images from 5 patients with grade IV glioblastoma.[38] They demonstrated that it was possible to accurately discriminate between normal tissue, tumor tissue, blood vessels and background by generating classification and segmentation maps in surgical time during neurosurgical operations, as shown in Figure 4.

In their second methodological paper[39], they used data from 6 patients with grade IV glioblastoma and applied improved algorithms to create maps, in which the parenchymal area of the brain could be delineated; an overall average accuracy of 80% was achieved.

Their HSI system was systematically assessed at two clinical institutions enrolling 22 patients, and researchers found that results relevant for surgeons were obtained within 15 to 70 seconds.[40] They also made available to the public this first *in vivo* hyperspectral human brain image database specifically designed for cancer detection. While authors were hopeful in their conclusion that HSI could facilitate brain tumor surgeries, no further studies beyond 2019 were published.

HSI files from the studies by Fabelo and coworkers are available from http://hsibraindatabase.iuma.ulpgc.es database.

## Entire gastrointestinal tract

During the past 3 years, the main focus of applying HSI in clinical oncology has been in the domain of the gastrointestinal tract, or more specifically, addressing anastomotic insufficiency, which is one of the most serious postsurgery complications of reconstructing the gastrointestinal conduit. As anastomotic healing fundamentally depends on adequate perfusion, HSI could be a suitable modality in assessing anastomotic perfusion in clinical practice. In a pilot study, Jansen-Winkeln *et al.*[41] collected hyperspectral images in 47 patients who underwent gastrointestinal oncologic resection followed by esophageal, gastric, pancreatic, small bowel or colorectal anastomoses. The recorded hyperspectral images were analyzed to extract the following specific physiological tissue parameters, which were deemed characteristic for perfusion changes at the sites of anastomoses: oxygen saturation of the tissue ($StO_2$), organ hemoglobin index (*OHI*), near-infrared perfusion index (*NIR-PI*), and tissue water index (*TWI*); the most clinically relevant appeared to be $StO_2$. They concluded that intraoperative HSI provided a noncontact, noninvasive modality, which enabled real-time analysis of potential anastomotic leakage without the use of a contrast medium. Their group followed their initial work with several studies focusing on the upper and lower gastrointestinal tract, respectively, described in more detail below.

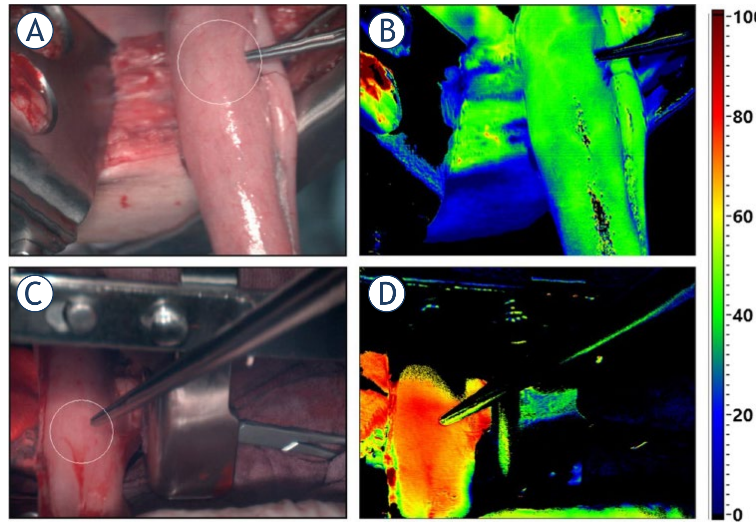


**FIGURE 5.** Comparison of Red-Green-Blue (RGB) images and near-infrared perfusion index (NIR PI) images recorded in a patient with **(A, B)** and without postoperative anastomotic insufficiency **(C, D)**.

Taken from Köhler *et al.*[9] and reprinted with permission from the publisher.

## Upper gastrointestinal tract

Köhler *et al.*[9] applied intraoperative HSI in 22 patients during esophagectomy to the tip of the gastric tube, which later became esophagogastric anastomosis; they compared physiological HSI parameters ($StO_2$, *OHI*, *NIR PI* and *TWI*) in 14 patients who underwent laparoscopic gastrolysis and ischemic conditioning of the stomach with those in 8 patients without pretreatment. They noted that the values of physiological HSI parameters were higher in patients with ischemic preconditioning than in patients without ischemic preconditioning; however, only $StO_2$ exhibited weak statistical significance. In a single patient who developed anastomotic insufficiency of the intrathoracic esophagogastric anastomosis, all physiological HSI parameters were substantially lower than those in


**FIGURE 6.** Hyperspectral imaging (HSI) acquisition system in the operating room. Hyperspectral images were acquired within a few seconds with physiologic HSI parameters displayed in false colors.

Taken from Moulla *et al.*[45] and reprinted with permission from the publisher.

other patients. Figure 5 compares the *NIR PI* image recorded in this patient with the corresponding image taken in the patient without postoperative anastomotic leakage. Hybrid esophagectomy along with intraoperative HSI used in the paper of Köhler *et al.*[9] was presented as a video article by Moulla *et al.*[42], while another clinical group[43] corroborated the findings of Köhler *et al.*[9] by reporting a case study including four patients.

Hennig *et al.*[44] continued the systematic evaluation of the capabilities of intraoperative HSI in 13 consecutive patients who underwent hybrid esophagectomy and reconstruction of the gastric conduit. Researchers also decided to use both intraoperative HSI and fluorescence imaging with indocyanine green (FI-ICG) to define the optimal position of anastomosis. While there are no threshold values yet established to define adequately and insufficiently perfused tissues, they decided that HSI physiological parameter $StO_2$ at >75% determined the well-perfused area. It was noteworthy that imaging modalities recorded simultaneously in 10 out of 13 patients identified the perfusion border zone more peripherally than the one designated subjectively by the surgeon. While HSI and FI-ICG may complement each other as intraoperative modalities, Hennig *et al.*[44] were of the opinion that HSI may be advantageous due to “the lower costs, noninvasiveness, and lack of contraindications”.

Moulla *et al.*[45] expanded oncological clinical applications in the domain of pancreatic surgery. Hyperspectral images were recorded during pancreatoduodenectomy in 20 consecutive patients before and after gastroduodenal artery clamping. In this pilot study, they were able to detect by the means of physiologic HSI parameter $StO_2$ improvement in liver perfusion after median acute ligament division in one patient with celiac artery stenosis. The HSI acquisition system in the operating room is shown in Figure 6.

## Lower gastrointestinal tract

Jansen-Winkeln *et al.*[9] applied intraoperative HSI in 24 patients to define the transection line during colorectal surgery. They found that the transection line subjectively delineated by the surgeon deviated from the border line determined by HSI; in 13 patients subjectively, planned resection was up to 13 mm too distal in the poorly perfused area, while in 11 patients, it was too far in the well-perfused area. Similar to esophagectomy[44], intraoperative HSI has shown potential in determining the optimal anastomotic area during colorectal surgery.

Jansen-Winkeln *et al.*[47] applied further intraoperative HSI along with FI-ICG in 32 consecutive patients undergoing colorectal resection and concluded that both modalities provided similar information in specifying the perfusion border zone and could complement each other. To optimize the performance of both modalities, Pfahl *et al.*[48] constructed the combined FI-ICG and HSI system, which was tested in 128 patients.

In another study[49], Jansen-Winkeln *et al.* imaged colorectal tumors in 54 consecutive patients during colorectal resections and found that HSI used in combination with a neural-network algorithm was able to classify cancer or adenomatous margins around the central tumor with a sensitivity of 86% and a specificity of 95%. Recently, they published a large study[50] enrolling 115 patients who underwent colorectal resection to systematically assess the feasibility of HSI in quantifying tissue perfusion, and in accordance with a smaller patient series, they found that "well-perfused areas were clearly distinguishable from the less perfused ones only after one minute".[46,47] Similar conclusions were reached in a group of 52 patients undergoing colorectal surgery by Barberio *et al.*[51], who also found that the physiological HSI parameter $StO_2$ was significantly lower in patients receiving neoadjuvant radio/chemotherapy than in other oncological patients. Figure 7 illustrates the usefulness of HSI in establishing the transection line during colorectal surgery.

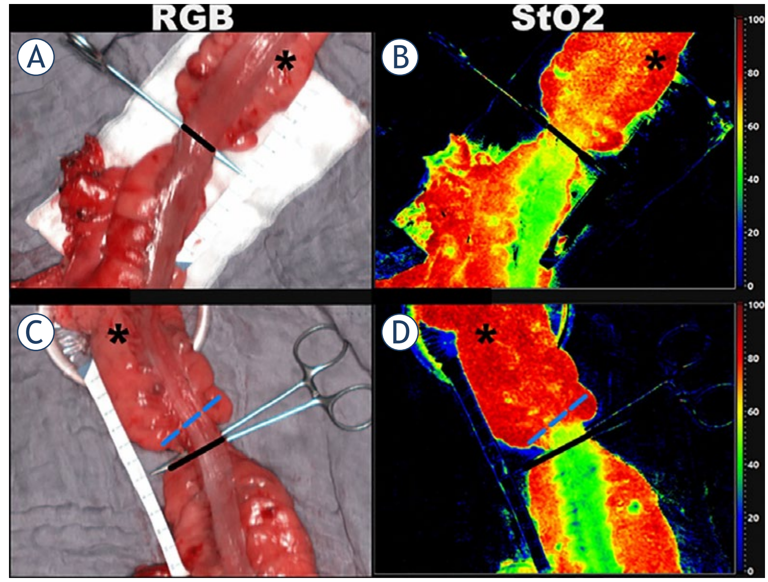


**FIGURE 7.** Usefulness of hyperspectral imaging (HSI) in establishing transection line during colorectal surgery. The Red-Green-Blue (RGB) image **(A)** and $StO_2$ map **(B)** show a patient in whom the clinical transection line (continuous line in black) and HSI transection line (dotted line in blue) were aligned; **(C)** and **(D)** show the RGB image and $StO_2$ map, respectively, of a patient in whom the clinical transection line deviated from the HSI transection line.

Taken from Barberio *et al.*[51] and reprinted with permission from the publisher.

## Discussion

Based on this literature review, the following inferences could be made: HSI is still finding its place in oncological clinical applications with the assessment of (i) mastectomy skin flap perfusion after breast reconstructive surgery[8] and (ii) anastomotic perfusion during reconstruction of gastrointenstinal conduit[9,44,45,48-50] as the most promising. However, caution needs to be advised because recently much research has been done in the arena of using HSI during brain surgery for glioblastoma, yet this clinical effort has not been sustained.

In addition, the need for an obvious expansion of the study of Pruimboom *et al.*[8] to a larger patient group, which would also include cases of DIEP flap necrosis, a meaningful and robust establishment of cutoff values for physiological HSI parameters is mandatory if HSI is to retain its clinical appeal. In their study, oxygen saturation of tissue $StO_2$ appeared to be the most useful HSI index, and the cut-off value of 36.3% predicting tissue necrosis was found; this value was close to that defined by a pilot study[52] enrolling mostly nononcological patients (19 out of 22), in which the values of both $StO_2$ and *NIR PI* above 40% indicated regular healing without any revision surgery; furthermore, operators in that study noted that HSI was superior to assessments based on clinical and Doppler ultrasound monitoring both in accuracy and speed. It is worthwhile to emphasize that HSI parameters are in general easy to follow by the operator as they are visualized as false-colour images (Figure 1).

When evaluating applications of HSI in assessing anastomotic perfusion during reconstructing gastrointestinal conduits, two main challenges become apparent: (i) the first challenge is, as in the case of breast reconstructive surgery, related to the establishment of a clear cutoff value indicating adequate tissue perfusion so that the operator can convincingly identify the optimal anastomosis area; (ii) the second challenge is related to HSI being limited to open surgery due to the large size of the HSI camera. The first challenge will need to be approached by enrolling progressively larger patient groups undergoing various oncological surgical interventions. It appears that the group of Jansen-Winkeln *et al.*[48,50] is already moving in this direction by conducting progressively larger clinical studies. However, with the application of neural networks, requirements for cohort sizes become far higher but could also be partially satisfied with the data augmentation. The second challenge has been recently addressed by the same group[15], with *ex vivo* testing of laparoscopic HSI camera and a highlight that the clinical trial with minimally invasive HSI has commenced already.

Comparison of HSI and FI-ICG[44,47,48] revealed similar results in defining the perfusion border of anastomosis, while both modalities were documented to be reliable, fast, and intuitive. Even if HSI is completely noninvasive, injection of ICG rarely provokes allergic reactions. Since there is a potential for each of the two modalities to contribute complementary information, it is not surprising that Pfahl *et al.*[48] constructed a combined HSI and FI-ICG recording system.

In conclusion, HSI is at this stage emerging as an attractive imaging modality to quantify perfusion in oncological patients. Hopefully, a larger number of clinical sites will initiate clinical trials to address the challenges, which still preclude the final acceptance of this promising imaging technique in the oncological clinical setting.

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