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MRI lymphography for esophageal sentinel node mapping: evolution of a NOTES technique

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ABSTRACT

MRI lymphography for esophageal sentinel node mapping: evolution of a NOTES technique.

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Introduction: The sentinel node (SN) concept may allow less invasive operation with selective lymphadenectomy, or in node negative patients, organ-preserving cancer resection by totally endoscopic techniques (e.g. endoscopic mucosal and submucosal dissection). Ideally the sentinel node is confined to a single node or lymphnode station such as in breast cancers and melanomas. In esophageal cancer, sentinel nodes mapping is feasible but complicated by multidirectional lymphatic drainage. As a result the clinical relevance of dye only guided mapping is limited and requires extensive dissection to accurately depict the entire node basin.

Aim: Having developed expertise in esophageal mural tunneling for the purposes of endoscopic Heller's myotomy, we are now exploring the feasibility of focused

esophageal SN identification and harvest using a combination of blue dye MRI lymphography.

Methods: Eight non-survival porcine models were used to demonstrate how targeted mediastinal lymph node biopsy could be performed trans-oesophageally by a combination of endoscopic submucosal lymphatic mapping, MRI imaging and NOTES. In the six pigs a lymphatic mapping of was performed by endoscopic submucosal injection of 2mls MRI contrast agent combined with methylene blue into the distal esophagus. This suspension of small molecular size dye particles is rapidly taken up by the submucosal lymphatic efferents and transported to the primary draining lymph nodes which are then detectable by their blue discoloration. A trans-esophageal submucosal tunnel is fashionedto access the mediastinumand visualize the blue-stained lymphatic vessels and lymph nodes for selective lymphadenectomy. The salient nodes are then retrieved via the esophagotomy and MRI scanned to confirm the presence of gadolinium in the colored nodes. In the 2 animals mapping was repeated as described above but instead of retrieving only the SN an en bloc esophagogastrectomy was performed to confirm that the SN basin distribution at MRI would match the blue dye lymphatic uptake.

Results: The operative technique proved readily feasible in all its aspects with blue sentinel nodes being visualized at MRI: the gadolinium followed the dye distribution assembling in the first draining node basin in all animals.

Conclusions: this very preliminary report suggests that MRI imaging may provide a new tool for systematic SN basin identification completely noninvasive requiring no preliminary aggressive dissection and without ionizing radiation. If proved sufficiently reliable, it may represent a step further towards an image guided solely endoscopic node harvest, diagnosis and resection of the primary tumor.

MRI lymphography for esophageal sentinel node mapping: evolution of a NOTES technique.

INTRODUCTION:

Flexible endoscopy is rapidly adapting itself to a laparoscopic, surgical, paradigm. Technological improvements of endoscopic platforms along with the constant development of techniques may constitute a giant leap toward minimal invasive therapeutic options for the treatment of upper GI cancers. Furthermore, new insights into physiology of the esogastric tract and new imaging modalities may provide a valid background for a truly minimally invasive image guided treatments. This innovative vision goes beyond the simple replication of open surgical procedures into a laparoscopic or endoscopic paradigm. . Minimally invasive oesophageal surgery is still relatively new and may represent an ideal research field to implement this new vision. Endoluminal and transluminal esophageal endoscopic procedures for both diagnostic and therapeutic purposes have recently been explored. To date multiple transesophageal endoscopic procedures, such as mediastinal lymph-node resection,[1-3] vagotomy,

sympatectomy thoracic duct ligation, thymectomy, [2] lung and pleura biopsy[1-4]epicardial coagulation, pericardial fenestration, and Heller myotomy have been described[1]. Haruhiro Inoue[5] has recently proposed one of the most attractive applications of the surgical endoscop reporting the ffirst clinical experiences of submucosal endoscopic esophageal myotomy for esophageal achalasia with a PerOral Endoscopic Myotomy (POEM) technique in 17 patients. The POEM was inspired by the works of Pasricha[6] and colleagues who, on the wave of NOTES, decribed the submucosal endoscopic esophageal myoyomy in an experimental setting. The POEM requires a selective division of the circular muscular bundles while leaving the outer longitudinal esophageal musculature intact. At our institution (IRCAD) we have been working on experimental models of endoscopic Heller's myotomy requiring oesphageal mural tunneling. A next sensible step has been to focus on the feasibility of targeted mediastinal explorative operations. One of the clues in minimal invasive oncologic procedure is the lymphnode harvesting for a precise staging. The ability to detect a sentinel node (SN) may allow for a less extensive procedure with a selective lymphadenectomy or for organ-preserving oncologic resections. Our aim was to develop a transesophageal NOTES technique for sentinel node (SN) mapping based on MRI lymphography.

NOTES and SN:

Natural orifice transluminal endoscopic surgery (NOTES) is considered to represent the next revolution in surgery. Many surgeons and endoscopists support the idea thatthat NOTES could represent a viable option in the treatment of early esophageal and gastric cancer, with a reduced surgical trauma. . This concept was first described by Cahill et al who proved the feasibility of lymphatic mapping and SN biopsy by NOTES for colon and gastric mapping in the animal model[7-9]. Lymphatic channel filling was immediately observable via the intraperitoneal optics. Although not yet appropriate for human use, this proposal merits serious consideration as a potential means of augmenting the effectiveness and appropriateness of ESD techniques for GI neoplasia. However, the main problem of full-thickness resection of gastric wall remains endoscopic gastric closure. Establishing an endoscopic suturing method would be an important step toward expanding potential indications. NOTES is met with both enthusiasm and skepticism but will gain its own place as human creativity eventually provides solutions to its technical limitations. In the near future, NOTES can evolve the capacity to complement the existing armamentarium for gastrointestinal cancer surgery. Ideally the sentinel node is confined to a single node or lymphnode station such as in breast cancers and

melanomas. Regarding upper gastro-intestinal cancers, sentinel nodes mapping is feasible but complicated by multidirectional lymphatic drainage. This is particularly true in esophageal cancer where a wide distribution and an unpredictable pattern of lymph node spread with multiple nodal station involved can be seen in up to 21% of patients. [10] As a result the clinical relevance of sentinel concept in the current treatment of patients with esophageal cancer is limited and requires extensive dissection to accurately depict the entire node basin. Dye only guided mapping would in fact entail an operative mobilization of the esophagus for real time observation of the lymphatic route, and mobilization itself could interfere with the lymphatic flow from the primary tumor. Reducing the extent of dissection needed to detect the sentinel node is a key advantage of the combined MRI imaging technique. MRI imaging may provide a new tool for systematic sentinel node basin identification completely noninvasive requiring no preliminary aggressive dissection and without ionizing radiation. If proved sufficiently reliable, it may represent a step further towards an image guided solely endoscopic node harvest, diagnosis and resection of the primary tumor.

GENERALITIES ON IMAGING MODALITIES AND CONTRAST AGENTS IN LYMPHNODE MAPPING:

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are the main clinically used modalities for lymph node staging.[11] The major drawback affecting both is that the use of radio-anatomical criteria only (shape and size) to determine the lymphnode status is not sufficiently reliable[12]. As an example, a recent metanalysis assessing the diagnostic precision of CT in staging of colon cancer has found an overall CT sensitivity and specificity for metastatic lymphnode detection of only 70% and 78% respectively[12]. Similarly, Non-enhanced MRI, although provides a better spatial resolution compared to CT, has limited value for nodal assessment with a sensitivity and specificity of 82.1% and 93.6% respectively, .[13]The use of a contrast compound that selectively accumulates in malignant structures may increase the precision of the lymphographic assessment. Two recent metanalysis assessed the performance of enhanced MRI in detection of lymphnode metastasis either by conventional endovenous Gadolinium administration[14] or endovenous Ultra Small Particles of Iron Oxide (USPIO) MRI[13] and the latter class of contrast showed a greater specificity and sensitivity in assessing the global nodal status. Several contrast agents and ways of administration have been assessed for this purpose. The

ideal lymphographic contrast agent has a tropism and rapid accumulation in nodes, a good systemic tolerance profile and a rapid clearance. Physical and chemical properties of the contrast compound influence the choice of administration route. The intravenous (IV) injection has some drawbacks such as the heterogeneous distribution between different lymphnode groups and no potential to detect the sentinel node. To overcome this limit, the possibility to perform a real time, intraoperative CT lymphography with endoscopic submucosal injection of CT contrast agent (Iopamidol) and laparoscopic tracking for sentinel node mapping has been assessed in oesophageal [15-16] and gastric[17, 18] cancer. Preliminary results with this new technique showed a sentinel node detection rate that varies from 30%[18] to 100%[16]. One of the possible explanations for the low detection rate could have been the rapid washout of the contrast.

In MRI enhanced lymphography, the most important administration routes are the IV but also the interstitial (i.e. peritumoral)[11]. Interstitial injection (subcutaneous or intracutaneous) has been described mainly for breast cancers, melanoma and head and neck cancers. The main advantage of this route is the extremely rapid uptake of the contrast agent into the lymphatic system (within few seconds) that may suggest a passive transport mechanism[19]

and the possibility to perform a real-time lymphography tracking the sentinel node. Furthermore, a lower dose of the agent may be used as compared to the IV injection. Most studied agents for interstitial injection MRI lymphography are[11]:

1) Extracellular contrast compounds (Gadolinium chelates): characterized by low toxicity, high thermodynamic and kinetic stabilities, rapid renal clearance and low specificity. Clinical available products are Dotarem® (Gadoterate Meglumine, Guerbet France), Magnevist® (Gadopentate Dimeglumine, Shering Germany), and Gadovist® (Gadobutrol, Shering Germany).

2) Superparamagnetic iron oxide particles (SPIO) : Ultrasmall particles of iron oxide (USPIO) constitute a contrast agent that accumulates in cells from the mononuclear phagocytic system. Approved product is Sinerem® (Ferumoxtran, Guerbet France), but since April 1st 2010 it is no more available in the market .To date no study has investigated the feasibility of a real-time MRI lymphography with endoscopic submucosal injection of either conventional extracellular compounds or USPIO to detect the sentinel node in the context of gastrointestinal neoplasm.

AIM:

Having developed expertise in esphageal mural tunneling for the purposes of endoscopic Heller's myotomy, we are now exploring the feasibility of focused esophageal SN identification and harvest using a combination of blue dye MRI lymphography.

MRI sentinel node navigation and mapping of colon, stomach and esophagus could provide an alternative truly "non" invasive diagnostic modality to identify node negative patients.

METHODS:

Non-survival porcine models were used to demonstrate how targeted mediastinal lymph node biopsy could be performed transoesophageally by a combination of endoscopic submucosal lymphatic mapping, MRI imaging and NOTES.

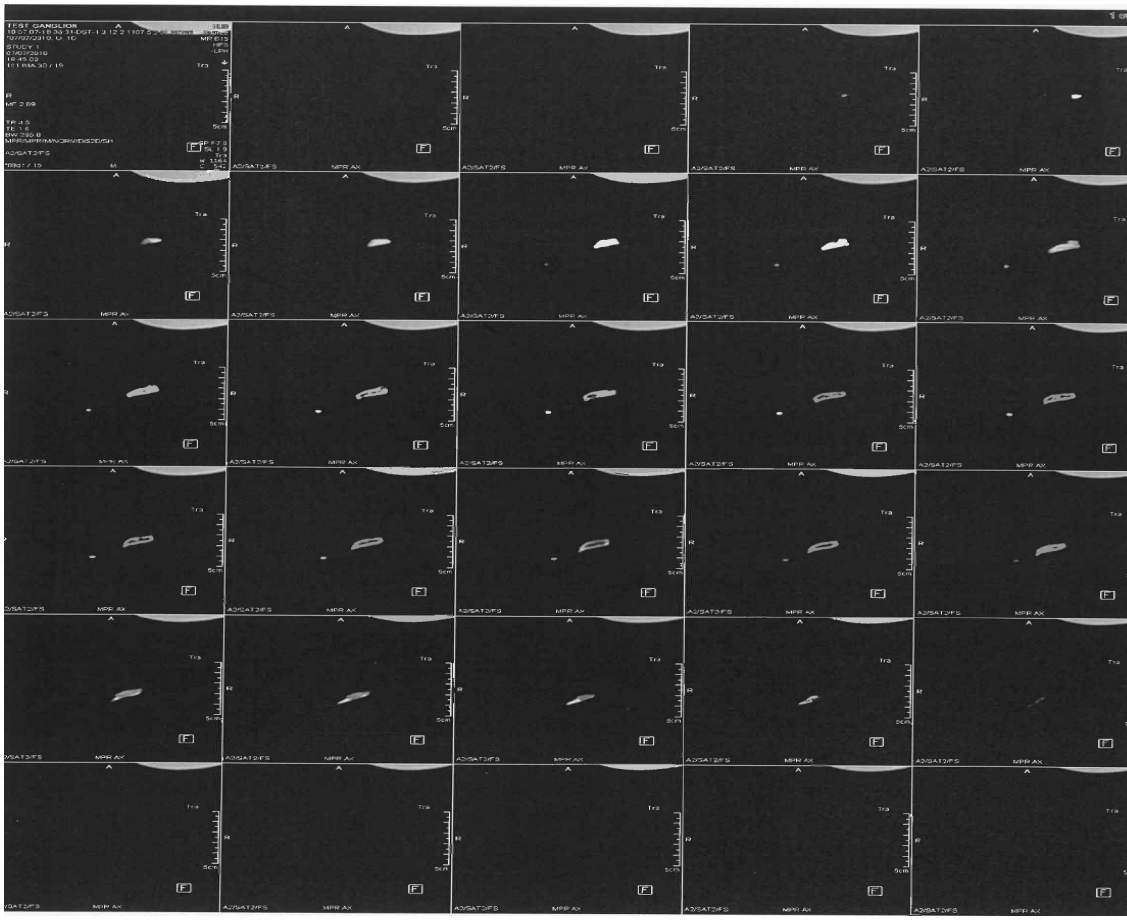
8 pigs were used and managed in accordance with both French laws for animal use and care and the European Community Council Directive No 86/609/EEC).

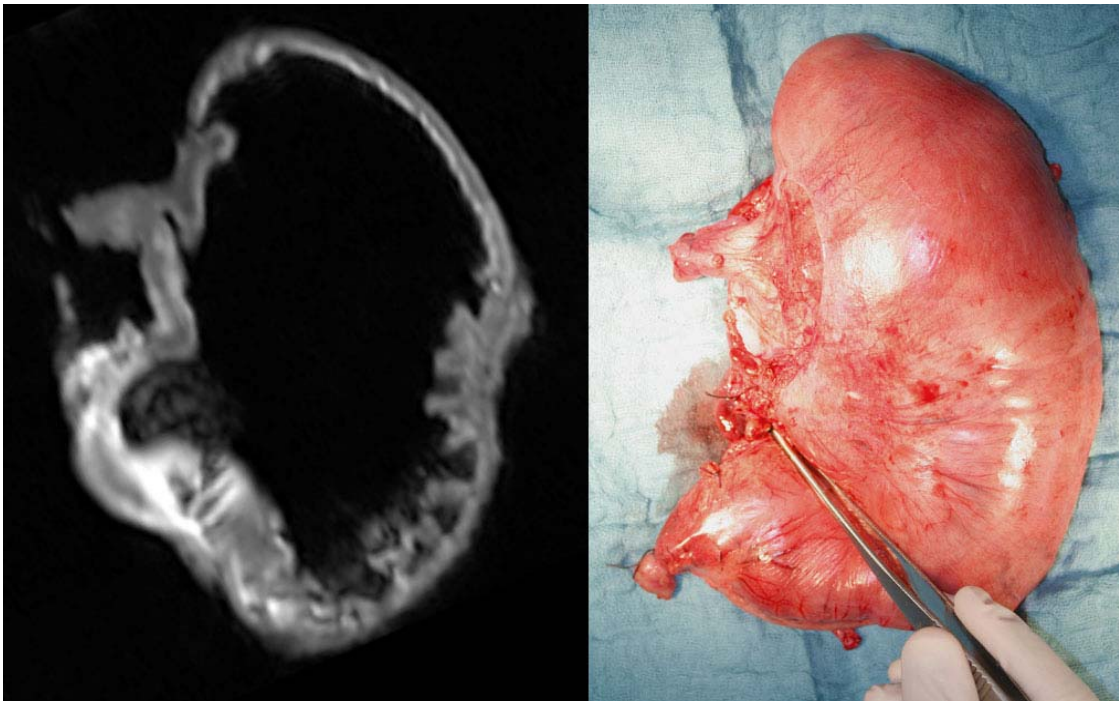
Preparation for surgery: Preoperatively each mini-pig was fasted for 24 hours. A premedication by intramuscular

injection comprising ketamine (7mls) and azaperone (3mls; Stresnil™, Janssen-Cilag, Belgium) was administered one hour before surgery while induction was achieved with intravenous proprofol (10ml/30 kg) combined with pancuronium (2mls). Anaesthesia is then maintained with 2% isoflurane after insertion of an endotracheal tube into the supine animal. All animals also receive copious cleansing of both the stomach (by gavage of 1.5 liters of water) and rectum (by water enemas until the effluent was observed to run clear).

In the six pigs, lymphatic mapping of the area of interest was performed by endoscopic submucosal injection of 2mls MRI contrast agent gadolinium combined with methylene blue into the distal oesophagus. This suspension of small molecular size dye particles was rapidly taken up by the submucosal lymphatic efferents and transported to the primary draining lymph nodes which were then detectable by their blue discoloration. A transesophageal submucosal tunnel was fashioned to enterthe mediastinum and visualize the blue dyed lymph nodes for selective lymphadenectomy. The nodes were then retrieved via the esophagotomy and MRI scanned to confirm the presence of gadolinium in the colored nodes (Fig 1) . In 2 experiments mapping was repeated as described above but instead of retrieving only the sentinel nodes an en bloc

oesophagogastrectomy was performed to confirm that the sentinel nodes basin distribution at MRI would match the blue dye lymphatic uptake (Fig 2). The gadolinium combined with methylene blue was found in the sentinel nodes in all animals.





RESULTS:

The operative technique proved readily feasible in all its aspects with blue sentinel nodes being visualized at MRI: the gadolinium followed the dye distribution assembling in the first draining node basin in all the animals.

CONCLUSIONS:

As emerging organ sparring techniques are established for early stage oesophageal tumours, less morbid resection and reconstruction techniques are also warranted. Today, the availability of sophisticated endoscopic tools and techniques in addition to physiology and imaging modalities should permit us to perform truly minimally invasive and precise image-guided treatments. Today, being less invasive needs to go further than laparoscopic or endoscopic replications of open surgical techniques. This novel technique has a potential as preoperative staging of sentinel node detection. We foresee several advantages: a very low dose of contrast to inject compared to the IV route, the possibility of being performed during a routinely diagnostic gastroscopy, the absence of exposition to radiation, and finally the possibility to manage early gastric cancer in the setting of Natural Orifices Transluminal Endoscopic Surgery including limited node retrieval. The future of NOTES lies not just in the reduction of the invasiveness of selected surgical procedures, but more in the development of innovative surgical concepts and revalidation of old surgical dogmas.

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