Ancillary N.O.T.E.S. procedures for early stage gastric cancer

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Abstract
The potential for performing truly scarless, safe surgery that at the same time may be less morbid is tempting both patients and physicians alike to seriously consider Natural Orifice Transluminal Endoscopy Surgery (NOTES) for a range of clinical applications. Given the move towards gastric-preservation by minimally invasive techniques for definitive management of early gastric cancer, this radical approach may find a niche within future clinical care paradigms for early stage malignant lesions of the stomach. Indeed already selected T1,N0 adenocarcinoma is being treated and even cured by advanced endoscopic techniques such as Endoscopic Submucosal Dissection. NOTES may initially therefore find a role in furthering the application of such endeavour by ensuring oncological providence in the treatment of those T1 lesions with higher risk of lymphatic metastases that currently are advised to lie outwith the scope of pure endoscopic resection (for reasons of oncological propriety rather than technical capacity). One such means NOTES could supplement ESD is by providing for direct sampling of sentinel nodes from the perigastric lymph basins. Subsequently perhaps a NOTES technique may develop capable of performing localized, full-thickness gastric wedge or sleeve resection for T2,N0 adenocarcinoma (and indeed perhaps other pathologies such as small gastrointestinal stromal tumors). This review examines how advancing technology along with progressive surgical thinking and innovation could lead to NOTES becoming absorbed into clinical care pathways for early gastric malignancy.

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Introduction

The general acceptance of laparoscopic surgery has made many operative procedures less invasive and thereby has been associated with reduced morbidity for the patient. With regard to gastric cancer, the laparoscopic approach was initially confined to diagnosis and concerned procedures geared towards preoperative staging [1]. Since then, increasing surgeon experience in combination with improved instrumentation and heightened patient expectation for less invasive treatments has resulted in its role being expanded to include therapeutic procedures [2,3]. Both surgical technology and technique have since proceeded further (again in tandem with patient expectations) and now Natural Orifice Transluminal Endoscopic Surgery (NOTES) is considered to represent the next revolution in surgery [4,5]. Although there has been as yet no clinical literature about early gastric cancer treated by NOTES procedures, the fact that Endoscopic Submucosal Dissective (ESD) techniques and indeed laparoscopic partial gastrectomy are already established in management paradigms suggests that, with technological and technique advances, NOTES may soon be sufficiently advanced to play a role in the address of certain pathologies.

In this article, therefore, we will discuss surgical treatment of early gastric cancer from the perspective of possible future roles for NOTES.

Early stage gastric cancer

The diagnosis of gastric cancer is usually made histologically from tissue biopsied at endoscopy. The depth of invasion however is first gauged using endoscopy and endoscopic ultrasonography and then confirmed by close scrutiny of the resected specimen. The presence of lymph node metastasis is currently analyzed with computed tomography, ultrasonography, and endoscopic ultrasonography. Early gastric cancer is defined by the Japanese Gastric Cancer Association classification system as a mucosal or submucosal invasive cancer (T1 cancer) irrespective of the presence of lymph node metastasis [6]. The diagnosis of early stage gastric cancer has increased worldwide in recent years although there are major differences in the proportion of early gastric cancer detected in Japan compared with the rest of the world. This difference is attributable to the well established nationwide screening program in operation in Japan which has increased the rate of early gastric cancer from 15% a few decades ago to 50% of all endoscopically diagnosed malignant lesions. In the West, however, where the low incidence of gastric cancer cannot justify a cost-effective screening program, the frequency of early gastric cancer has only increased from 10% to 15–20% over a similar time-frame [3].

Since 5-year survival rates of primary stage IA gastric cancer after standard gastrectomy with D2 dissection already exceed 90%, improving the quality of life after definitive treatment (while preserving high survival rates) is the next hurdle in the surgical care of these lesions. To further this concept, Guidelines for Gastric Cancer Treatment were published in 2001 [7] and since revised in 2004 [8]. These recommendations are very useful for ensuring correct clinical application of the available treatments. The guideline for early gastric cancer in tertiary and academic research centers is shown in Table 1. With N2 or N3 early gastric cancer being rare, it can be appreciated that early gastric cancer currently falls nearly entirely under the remit of endoscopic resective techniques and laparoscopy. NOTES could perhaps occupy the ‘middle-ground’ between these lesions.

Minimal access surgery and early stage gastric cancer

Recent literature and experience certainly suggests possibilities for preliminary clinical applications for natural orifice surgery for diagnostic purposes in the near future. A secure means of visceral access closure is essential for this to proceed within the exception of transvaginal access (which already can be safely and securely rejoined by simple suturing). Technological advances seem likely to overcome this issue for the colon, stomach and bladder in the near future. Similar progress with instrumentation seems likely also to facilitate the performance of gastroenteral anastomosis from within the bowel (as has already been proposed) and therefore NOTES peritoneoscopy for cancer staging could also in time represent an option of treatment for advanced gastric cancer [37,38].

However with specific regard to early gastric cancer, a more nuanced approach to patients may be possible thanks to the revolution in perception as much as access that may be provoked by NOTES. Therefore the following sections discuss and deliberate how NOTES may be used in combination with standard minimal access techniques for these lesions.
Endoscopic dissection and NOTES

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are advanced therapeutic endoscopic techniques and may be considered the ultimate ‘minimum’ invasive treatments for early stage gastric cancers. Both are relatively new with ESD commencing about 10 years ago for superficial gastrointestinal neoplasms. Many ESD skills now performed by endoscopists will have a great influence on the practice of NOTES and so NOTES proponents have a great deal to learn from ESD practitioners. In return, NOTES can contribute to the practice of ESD by providing for means of performed secure gastric closure at the time of the accidental perforation without recourse to standard surgical operation.

According to the "Gastric Cancer Treatment Guidelines" the appropriate indication in patients with early gastric cancer is limited to lesions with a minimal chance of lymph node metastasis and a size that allows en bloc excision [8]. The optimal lesion for ESD is thought to be an intramucosal differentiated-type adenocarcinoma without ulceration or scarring that is 20 mm or less in size, regardless of macroscopic type. At present, lesions with preoperative endoscopic diagnosis of differentiated-type intramucosal cancer without ulcer findings, differentiated-type intramucosal cancer no longer than 3 cm in diameter with ulcer findings, differentiated-type minute invasive submucosal (less than 500 μm below muscularis mucosa) cancer no longer than 3 cm in diameter are considered expanding indication for ESD [16,17]. On pathological analysis of primary T1 lesions confined to the submucosa, the conditions of no lymph node metastasis are that SM1, ly0, v0 and ±30 mm. Patients at risk of lymph node metastasis should undergo gastrectomy and lymph node dissection for T1 cancer.

However, the actual technical capacity of ESD manifestly exceeds these indications. Furthermore, even though the risk of nodal metastases has increased relatively, the absolute percentage of LN metastasis of this group is still actually low (i.e. most patients in these groups do not have lymph node dissemination [18–20]). Finally, much of the histological information supporting the performance of ESD is available only after the primary lesion has been resected. NOTES might be able to build a bridge between ESD and Standard D2 gastrectomy.

Sentinel node navigation surgery

Recently, a growing number of clinical trials evaluating the feasibility and accuracy of sentinel lymph node biopsy in gastric cancer have been published [21–23]. However the lymphatic drainage of stomach is considerably more complex than that of ectodermal organs like breast and skin due to the complex embryological development. So, the application to sentinel lymph node concept in gastric cancer is still under discussion. Although the accuracy and reliability of sentinel node navigation is similar in levels at least in selected centers in their literature [24,25], this theory has yet to be definitively proven. Furthermore, as lymphatic mapping itself becomes less accurate with advancing disease, as is the case with melanoma as well as breast and colon cancer. Therefore the very lesions it works best in are those most suitable for endoscopic resective techniques [24].

NOTES may provide for endoscopic sentinel node biopsy as a complement and oncological augment to current ESD technique. We have proven the technical feasibility of lymphatic mapping and sentinel node biopsy by NOTES for the stomach in pig model [26].

If sentinel nodes theory is demonstrated convincingly (and the results of large multicenter trials from Japan are awaited with great interest), the following procedures are theoretically feasible as a new standard treatment for early gastric cancer currently excluded as the indication of ESD (i.e. sm2, sm3, sm1 with undifferentiated-type or ulcer), NOTES sentinel node biopsy (negative); combined with ESD,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Treatment options according to stage for gastric cancer.</th>
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<tr>
<td></td>
<td>NO (stage IA)</td>
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<tr>
<td>Mucosal T1 cancer (≥2.0 cm)</td>
<td>EMR (piecemeal resection)</td>
</tr>
<tr>
<td>Submucosal T1 cancer</td>
<td>Wedge, segmental resection</td>
</tr>
</tbody>
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Extended surgery (dissection) = Extended gastrectomy with extended lymphadenectomy.
Extended surgery (combined resection, dissection) = gastrectomy with combined resection of involved organs and extended lymphadenectomy.
EMR = Endoscopic mucosal resection; ESD = Endoscopic submucosal dissection.
Iatric character is inserted by author.
EMR, wedge resection, or pylorus-preserving gastrectomy. NOTES sentinel node biopsy (positive); convert to the laparoscopic or open D2 gastrectomy. To maximize the utility of the technique, reliable intraoperative analysis of the sentinel nodes is required.

Laparoscopy and NOTES

Since its first report in 1994, laparoscopic-assisted distal gastrectomy has been widely adopted for early gastric cancer and the number of patients undergoing it has been increasing. At present, T1/T2, N0 gastric cancer is considered the only indication for laparoscopic gastrectomy [13]. Laparoscopic-assisted gastrectomy can be either partial (i.e., distal or proximal gastrectomy) or total gastrectomy at least in selected centers [9–12]. However, LADG remains controversial as a standard surgery for gastric cancer because there are as yet few studies evaluating its technical difficulty, advantages, and oncological feasibility.

Initially, NOTES may be proposed to help the surgeons reduce the number of transabdominal trocars. Transvaginal, transcolonic, or transvesical routes might be good candidates for access route to the stomach in order to perform so-called “hybrid NOTES”. Indeed several centers have already reported sleeve gastrectomy assisted by NOTES [14,15]. Similar methods might therefore be applicable to partial or wedge resection for the primary lesion alone in the case of small, early gastric cancer with the resected specimen then being removed the organ breached. Certain Gastrointestinal Stromal Lesions (GIST) may also be resectable by such approaches. Potentially also, Magnetic Anchoring and Guidance systems may also be enrolled to further reduce trocar number with the magnetic component with the viscus being removed within the specimen.

Although, a transgastric route seems attractive given that it could be used in both genders and that the gastroscope can also be used for both organ resection and retraction, the transgastric route may be viewed unacceptable by surgeons and endoscopists because of concerns regarding oncological safety given that endoscope penetrates back and forth through the cancer-containing organ. Therefore it would seem most prudent to resect cancerous lesion before entering the abdominal cavity, subsequently, NOTES lymph node sampling for analysis and even dissection could be performed via the resection site although further technical refinement is required before en bloc lymphadenectomy can be performed.

Future perspective of NOTES

However, given the relative technical complexity of partial gastrectomies, NOTES is unlikely to directly challenge laparoscopic means of performing sentinel node biopsy in the near future. At present, sentinel node biopsy seems an ideal indication for NOTES as a means of supplementing the oncological providence of endoscopic resective techniques.

Any closure of a full-thickness gastric access must of course be absolutely reliable if NOTES is to applied in early gastric cancer. Several centers have reported gastric closure methods including not only intentional gastric perforation but also iatrogenic perforation. Tissue anchors [27,28], endoscopic clips [29], suction-based prototype sputuring device [30–33], and other instruments [34–36] have all been reported however, no-one method has yet been universally accepted or adopted. Tremendous efforts to establish perfect closure methods are therefore ongoing.

Once dependable suture devices are available, NOTES gastrojejunostomy from within the stomach may have a role for palliation of advanced cancer. To expand the indication for curable advanced gastric cancer however, there is no doubt, lymph node dissection is mandatory. Lymph node dissection by flexible scope will be one of the most challenging or difficult part to establish perfect NOTES gastrectomy for early gastric cancer. Probably we need to wait until completely new and/or robotized instruments become available to overcome the current drawbacks of NOTES approaches (i.e., lack of triangulations, retraction, exposure, and scope stability issue). Indeed most of the circumstances surrounding NOTES at present will likely dramatically change both with technological and instrument refinement through the concerted efforts of not only surgeons and endoscopists but also mechanical engineers.

Conclusion

NOTES is faced with both enthusiasm and skepticism but will gain its own place in the field of surgery sooner or later as human creativity can be trusted to eventually provide solutions to its technical limitations. In near future therefore, we believe, that NOTES can evolve the capacity to compliment the existing armamentarium for gastric cancer surgery.

Conflict of interest statement

None of the authors have any conflict of interest to declare.

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References

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