

Horizon Scanning in Surgery: Application to Surgical Education and Practice

Cryotherapy for Esophageal Cancer

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Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Acronyms

AC	Adenocarcinoma
APC	Argon plasma coagulation
BE	Barrett's esophagus
EMR	Endoscopic mucosal resection
ESD	Endoscopic sub-mucosal dissection
FDA	Food and Drug Administration (United States)
GERD	Gastro-esophageal reflux disease
HGD	High grade dysplasia
IMCA	Intra-mucosal carcinoma
LGD	Low grade dysplasia
MPEC	Multipolar electrocoagulation
NICE	National Institute for Health and Clinical Excellence (United Kingdom)
PDT	Photodynamic therapy
PET	Positron emission tomography
PPI	Proton pump inhibitors
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
SCC	Squamous cell carcinoma

Introduction

Background

There are two types of esophageal cancer as determined by the histopathology of the disease:

- Squamous cell carcinoma (SCC) which commonly occurs in the proximal to middle parts (upper two thirds) of the esophagus.
- Adenocarcinoma (AC) which commonly occurs in the distal part (lower third) of the esophagus and gastro-esophageal junction.

In general, SCC is the most common type of esophageal cancer, despite the incidence of AC rapidly increasing in Europe and the US during the last decade (Lambert and Hainaut 2007).

The cause of esophageal cancer is unknown; however, a number of risk factors have been identified for both SCC and AC. Barrett's esophagus (BE) is one of the major risk factors associated with the development of esophageal cancer. BE commonly results from repeated caustic injury arising from chronic gastro-esophageal reflux disease (GERD) (Garcia et al 2007). Esophageal cancer is 30 to 120 times more common among patients with BE, compared to the general population (Sikkema et al 2010). BE describes a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy (Wan and Sampliner 2008). The transdifferentiation of squamous epithelial cells into columnar epithelial cells is known as metaplasia. The risk of BE developing into cancer further increases if dysplasia is present (Wani et al 2009). Dysplasia is an early stage of a cancerous process where abnormally developed immature cells exceed the number of mature cells. The risk of esophageal cancer in patients with low grade dysplasia (LGD) is low (about 1% per patient year) compared with high grade dysplasia (HGD) (over 10% per patient year) (Shaheen et al 2009). Most commonly, the squamous cell epithelium proximal to the gastro-esophageal junction is affected which leads to esophageal AC. However, despite the association between BE, GERD and esophageal cancer, it is possible for patients to present with invasive esophageal cancer without any preceding reflux symptoms (Bancewicz 2004).

Other risk factors associated with esophageal cancer include smoking, alcohol intake, achalasia, and consequences of a sedentary lifestyle such as obesity, dietary deficiencies (due to low fruit and vegetable intake), and genetic factors (Umar and Fleischer 2008). The incidence of the disease is notably higher among males who are over 65 years of age.

Like many other cancers, early diagnosis is the key to cure in esophageal cancer. According to the American Joint Committee on Cancer, TNM staging^{*} of the disease determines whether the intent of the therapeutic approach will be curative or palliative (Greene et al 2002). LGD is difficult to detect by endoscopy and the majority of HGD is only diagnosed endoscopically during its later stages. Therefore, because of the often delayed diagnosis, the majority of patients diagnosed with esophageal cancer are not candidates for surgery (Shaheen et al 2010). In fact, at diagnosis, approximately 50% of patients with esophageal cancer will have metastatic disease and will therefore be candidates for palliative rather than curative care (Enzinger et al 1999).

^{*}TNM staging is based on the number and size of the primary tumor (T), the extent of the spread to nearby lymph nodes (N) and the presence of metastases (M).

Esophageal cancer can spread locally or systemically. The loco-regional mechanism of disease spread can lead the cancer into neighboring structures along the esophagus and to regional lymph nodes. Any organ can be affected by the systemic spread of the disease; however, metastases to the liver and lung most commonly occur (Bancewicz 2004).

Esophagectomy is the gold-standard treatment in curing early stage esophageal cancer and the only effective intervention that may stop the progression of dysplastic BE to invasive cancer (Hudson et al 2011). Ongoing medical treatment, anti-reflux medication including proton pump inhibitors (PPIs), chemotherapy and radiotherapy play an important role in the management of esophageal cancer, in addition to curative resection. Generally, radiotherapy alone is indicated for SCC, while chemoradiotherapy is indicated for AC (Bancewicz 2004).

Ablation modalities are another treatment option and are less invasive than esophagectomy. Such ablation techniques include endoscopic mucosal resection (EMR), endoscopic sub-mucosal dissection (ESD), argon plasma coagulation (APC), multipolar electrocoagulation (MPEC), laser ablation (using neodymium-yttrium aluminum garnet (Nd-YAG), potassium titanium phosphate), photodynamic therapy (PDT) and radiofrequency ablation (RFA).

Cryotherapy is one of the most recent ablation techniques that has been used in the management of BE and esophageal cancer (Gaddam and Sharma 2010). Patients who are ineligible for conventional curative resection due to underlying comorbidities of advanced cancer may benefit from this endoscopic treatment modality. While the use of cryotherapy for esophageal cancer is relatively recent, it has been used for some time in the treatment of glottic and subglottic stenosis, radiation proctitis, and for skin conditions such as warts (Krimsky et al 2010; Hou et al 2011).

Burden of disease

Esophageal cancer accounts for approximately 1% of all cancers and 6% of cancers involving the gastrointestinal tract. The disease is three to four times more common in males than in females (Garcia et al 2007). In 2010, it was estimated that there were 16,400 new esophageal cancers in the United States (US), of which 13,130 (80%) were male. In the same year, it was estimated that 11,650 males would die from the condition (Howlader et al 2010; National Cancer Institute 2011). In the US, the mortality rate associated with esophageal cancer in males increased by 10.9% from 1990 to 2005 (National Cancer Institute 2011).

The prognosis of this disease is worse than most other cancers, with a recent study reporting a median survival of only nine months (Willett and Czito 2009). According to the American Cancer Society, the five year survival rate for esophageal cancer in the US can be as low as 17% if the cancer is diffuse or metastatic at the time of diagnosis, and as high as 37% for low grade, localized cancer (American Cancer Society 2007).

The National Cancer Institute estimated the cost of treating esophageal cancer in the US in 2006 to be approximately US\$1.1 billion, out of a total of US\$104.1 billion for all cancer related medical expenditure in the same year (National Cancer Institute 2009).

Technology

Cryotherapy employs thermal ablation to treat esophageal cancer and BE. Ablation is achieved by intracellular disruption and ischemia that is produced by freeze-thaw cycles using liquid nitrogen or carbon dioxide (Gaddam and Sharma 2010). Specifically, these cycles of rapid freezing and slow thawing destroy tissue through the formation of extracellular and intracellular ice, which disrupts cell membranes and processes, and tissue ischemia through vascular stasis from decreased blood flow, endothelial damage and, ultimately, vascular thrombosis (Greenwald and Dumot 2011). This technique preserves the extracellular matrix and therefore promotes less fibrosis (Gaddam and Sharma 2010).

Cryotherapy is typically performed as an outpatient or day surgery procedure, and the patient is usually able to return to their normal activities the following day. Patients are generally prescribed a high dose of PPIs for seven days before the procedure to maintain low stomach acidity. During the procedure, a spray catheter introduced through the working channel of an endoscope is used to deliver a targeted spray of liquid nitrogen or carbon dioxide to the dysplastic or non-dysplastic epithelium, which initiates the freeze cycle (Gaddam and Sharma 2010). In order to facilitate the escape of excess nitrogen out of the body, and thus prevent any perforation of gastrointestinal viscus, an orogastric tube is introduced. Treatment is then interrupted for a few minutes to enable the tissue to thaw. This cycle is then repeated a number of times to complete a treatment session (Gaddam and Sharma 2010). The effectiveness of the treatment depends on the lowest tissue temperature achieved, the number of freeze-thaw cycles and the duration of each freeze and thaw cycle. Most commonly, 2-4 cycles of 20 seconds of liquid nitrogen or 4-8 cycles of 10-15 seconds of carbon dioxide are administered (Greenwald and Dumot 2011). Repeat sessions may be necessary until the entire dysplastic esophageal lumen is replaced by a healthy lining, with an average of 3-4 sessions required, including a break of 6-8 weeks between sessions (Halsey and Greenwald 2010). The prolonged duration of treatment and fogging of the endoscopic lens during the procedure (due to evacuation of moist air from the distal end of the endoscope) are some of the limitations of the technology (Gaddam and Sharma 2010).

Common post-procedural adverse events include pain and dysphagia (Halsey and Greenwald 2010). Other potential complications include pulmonary aspiration of stomach contents, strictures, hemorrhage and esophageal perforation. Esophageal cryotherapy is contraindicated for patients with mucosal breaks, eosinophilic esophagitis or coagulopathy. The treatment is also not recommended for patients with anatomical alterations of the esophagus, or those who have undergone gastric bypass surgery. If gastric contents are visualized at the time of treatment, the procedure should be rescheduled. Esophageal cryotherapy should not be used during pregnancy due to the lack of evidence evaluating its safety in this setting (Chen and Pasricha 2011).

Stage of development

There are a large number of cryosurgical devices that have been approved for use by the US Food and Drug Administration (FDA); however, the two main commercially available devices for endoscopic spray cryotherapy in the gastrointestinal tract are the CryoSpray Ablation System manufactured by CSA Medical Inc (Baltimore, Maryland, US), and the Polar Wand Cryotherapy System manufactured by the GI Supply division of Chek-Med Systems Inc (Camp Hill, Pennsylvania, US).

The CryoSpray Ablation System was approved for use by the FDA in 2007 (07/12/2007; 510(k) no: K072651) (FDA 2007), and is the device that has been used in the majority of published trials investigating the use of cryotherapy for BE and esophageal cancer. This device releases low pressure (2-3 psi) liquid nitrogen at -196°C. It is comprised of a large console containing the liquid nitrogen, a catheter with an insulated coating (allowing the catheter shaft to remain at or near ambient temperature maintaining its pliability) that is passed through the working channel of a standard endoscope, and a foot pedal for release of nitrogen (Rodriguez et al 2008). In addition, a separate orogastric or nasogastric tube located next to the endoscope is required in order to evacuate the rapidly expanding, evaporated nitrogen gas during the procedure (Greenwald and Dumot 2011).

The Polar Wand Cryotherapy System was approved for use by the FDA in 2002 (31/07/2002; 510(k) no: K021387) (FDA 2002). This method employs the Joule-Thompson effect, in which rapidly expanding carbon dioxide gas produces cooling to -78°C (Greenwald and Dumot 2011). The device consists of a small cylinder containing the carbon dioxide, which is pressurized to 450 to 750 psi, a 6F, 200-cm-long, single-use catheter, and an evacuation tube that attaches to the tip of the endoscope to remove gas from the gastrointestinal tract (Rodriguez et al 2008). The release of carbon dioxide and concurrent activation of the evacuation tube is controlled with a foot pedal (Rodriguez et al 2008).

A search uncovered three clinical trials currently underway, and two trials that have been completed but for which no published data are yet available (ClinicalTrials.gov 2012) (Table 1).

Table 1: Clinical trials underway for Cryotherapy for BE and esophageal cancer

Trial ID	Title	Study design	Estimated completion date
NCT00650988	A pilot study of cryotherapy for BE with HGD and early esophageal cancers	Non-randomized	January 2011
NCT00628784	Endoesophageal cryotherapy for ablating BE and early stage esophageal cancer	Non-randomized	March 2012
NCT01293448	Evaluation of balloon-based cryoablation of human esophageal epithelium	Non-randomized	June 2012
NCT00754468	Study of CryoSpray Ablation to determine treatment effect, depth of injury, and side effects in the esophagus	Randomized	December 2012
NCT00747448	CryoSpray Ablation GI patient registry	Observational	December 2014

BE: Barrett's esophagus
 GI: gastrointestinal
 HGD: high grade dysplasia

Current treatment and alternatives

Esophagectomy, which effectively removes the cancerous esophagus and replaces it with a gastric or colonic conduit, is the gold-standard treatment for curing early stage esophageal cancer (Hudson et al 2011). The mortality rate associated with this procedure has been reported to be between 1% and 10% (Fernando et al 2009; Lalwani 2008; Sgourakis et al 2010; Sharma 2009),

with a recent study reporting that perioperative mortality rates have fallen to between 3% and 5% (Stavrou et al 2010). However, the morbidity rate associated with esophagectomy remains high, ranging between 30% and 50%, while the quality of life for patients following the procedure is impaired compared with those with an intact esophagus (Gan and Watson 2010). A number of minimally invasive surgical approaches, including combinations of laparoscopic and thoracoscopic techniques, trans-hiatal and three-stage procedures, have been developed in an attempt to tackle the morbidity and quality of life issues associated with esophagectomy (Gan and Watson 2010). Specifically, these techniques aim to improve the rate of recovery and quality of life following the procedure by reducing the size of the incisions used during surgery, and thus the rate of wound-related complications (Gan and Watson 2010). The high morbidity rate following esophagectomy has also stimulated the development of newer endoscopic treatments, including ablation and mucosal resection, which preserve the esophagus (Gan and Watson 2010). Commonly used endoscopic treatments include:

- endoscopic mucosal resection;
- argon plasma coagulation;
- photodynamic therapy;
- radiofrequency ablation.

Endoscopic mucosal resection (EMR)

Endoscopic mucosal resection (EMR) involves the local excision of a large area of mucosa up to the depth of submucosa. This technique has been used to remove discrete mucosal nodules in patients suffering from BE with HGD or intramucosal carcinoma (IMCA), as well as to excise complete segments of metaplastic mucosa (Fernando et al 2009). A number of approaches have been used to achieve EMR, including strip biopsy, inject and cut, cap-assisted EMR, and ligate and cut (Gaddam and Sharma 2010). One of the main advantages of EMR compared with other ablative procedures is that it provides tissue specimens that can be used for histological assessment, and can therefore be classified as both a diagnostic tool and therapeutic option (Gaddam and Sharma 2010). This procedure is not appropriate for patients with coagulation disorders or portal hypertension, and is difficult to perform in the presence of longer segments of BE, or in the absence of an endoscopically visible lesion (Gan and Watson 2010). Complete resection rates of between 80% and 90% have been reported in most studies, although long-term studies have demonstrated a significant risk of recurrence (Gan and Watson 2010). Commonly reported complications include bleeding and late stricture formation, which occur in approximately 15% of procedures (Gan and Watson 2010).

Argon Plasma Coagulation (APC)

In argon plasma coagulation (APC), coagulation of the dysplastic mucosa is achieved using an electric current that is conducted through a jet of argon gas (Gaddam and Sharma 2010). During the procedure argon gas flows via a catheter that is passed through the working channel of the endoscope and a high voltage is then applied (Gaddam and Sharma 2010). APC is inexpensive and widely accessible, and can be used as a primary therapeutic option or in addition to other treatment modalities. The procedure has been used for the treatment of early neoplasia, as well as for palliation of more advanced cancers; however, the longer-term outcomes following APC treatment of early cancer are inconsistent. Complications that can occur following APC include pain, ulceration, bleeding and strictures, which have been reported in up to 24% of procedures;

however, mortality is rare (Gan and Watson 2010). It has been suggested that the role of APC is likely to diminish as other techniques such as EMR and RFA begin to be used more widely (Gan and Watson 2010).

Photodynamic therapy (PDT)

In photodynamic therapy (PDT), free radical oxygen is used to destroy cells. Firstly, an intravenous photosensitizer such as porfimer sodium or 5-aminolevulinic acid is administered, which selectively accumulates in neoplastic esophageal mucosal cells (Fernando et al 2009). This is followed by target tissue activation of the photosensitizing agent by exposing the BE mucosa to either bare cylinder or balloon-based diffusing light fibers introduced through the endoscopy accessory channel (Gaddam and Sharma 2010). Free oxygen radical formation results, which in turn causes cell apoptosis. PDT has been used to treat dysplastic BE and intramucosal cancer; however, it is associated with a significant recurrence rate at long-term follow-up (Gan and Watson 2010). In addition, the procedure is associated with the development of complications such as esophageal stricture and cutaneous photosensitivity (Fernando et al 2009).

Radiofrequency ablation (RFA)

Radiofrequency ablation (RFA) is a relatively new technique that involves the application of thermal energy to BE mucosa. The procedure involves the use of a balloon-based catheter (capable of treating large circumferential areas) or a probe-based catheter (commonly used to treat small areas of BE) to deliver a high-power, ultra-short burst of ablative energy to the abnormal esophageal epithelium (Gaddam and Sharma 2010; Fernando et al 2009). The precise and automated delivery of a preset amount of standardized radiofrequency energy makes this technique simpler and less-time consuming than other ablative modalities (Gaddam and Sharma 2010). RFA is associated with a high rate of complete eradication in the treatment of dysplastic and non-dysplastic BE, while the rate of esophageal stricture following the procedure is low (Gan and Watson 2010). Long-term follow-up data from patients treated with RFA are required in order to confirm the procedure's utility.

Literature review

Search criteria

Keywords/MeSH terms utilized:

Esophageal cancer (MeSH), Barrett's esophagus (MeSH), barrett*, cryoablation, cryospray, cryosurgery, cryotherapy

Databases utilized:

PubMed, EMBASE

Inclusion criteria

Table 2: Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Randomized controlled trials, non-randomized comparative studies and case series studies
Patient	Patients with Barrett's esophagus and esophageal cancer
Intervention	Cryotherapy
Comparator	Ablation modalities including laser therapy, PDT, APC, EMR, ESD, MPEC and RFA
Outcome	Safety: adverse events Efficacy: endoscopic and histological eradication of Barrett's esophagus and esophageal cancer
Language	English only

APC: argon plasma coagulation
EMR: endoscopic mucosal resection
ESD: endoscopic submucosal dissection
MPEC: multipolar electrocoagulation
PDT: photodynamic therapy
RFA: radiofrequency ablation

Included studies

No randomized controlled trials (RCTs) or non-randomized comparative studies were identified. A total of six case series studies were selected for inclusion in this report (Table 3). All six studies assessed the use of endoscopic spray cryotherapy, using the CryoSpray Ablation System, for the treatment of BE and/or esophageal cancer.

Table 3: Characteristics of included studies

Study/Location	Level of evidence (Appendix A)	Intervention* and number of patients
Barthel et al 2011 <i>United States</i>	Level IV Case series	Endoscopic spray cryotherapy (n=14)
Greenwald et al 2010a <i>United States</i>	Level IV Case series	Endoscopic spray cryotherapy (n=79)**
Greenwald et al 2010b <i>United States</i>	Level IV Case series	Endoscopic spray cryotherapy (n=77) [#]
Shaheen et al 2010 <i>United States</i>	Level IV Case series	Endoscopic spray cryotherapy (n=98) [¶]
Dumot et al 2009 <i>United States</i>	Level IV Case series	Endoscopic spray cryotherapy (n=30) [§]
Johnston et al 2005 <i>United States</i>	Level IV Case series	Endoscopic spray cryotherapy (n=11) [†]

*All studies used the CryoSpray Ablation System

**Of the 79 patients enrolled, 49 had completed treatment at the time of data collection and were included in the efficacy analysis. All 79 patients were included in the safety analysis.

[#]Of the 77 patients enrolled, 24 had completed treatment at the time of data collection and were included in the efficacy analysis. All 77 patients were included in the safety analysis.

[¶]Of the 98 patients enrolled, 60 had completed treatment at the time of data collection and were included in the efficacy analysis. All 98 were included in the safety analysis.

[§]A total of 39 patients were enrolled in the study, and 37 patients received treatment with cryotherapy. Of these 37 patients, seven were excluded, and 30 patients were included in the safety and efficacy analyses.

[†]A total of 11 patients were enrolled in the study, and all received treatment with cryotherapy. Of these 11 patients, one failed to complete the study due to a large hiatal hernia which precluded the ability to completely eradicate his Barrett's esophagus, and another failed to complete the study due to severe arthritis predating study enrollment. A total of nine patients were included in the efficacy analysis, and all 11 patients were included in the safety analysis.

Study profiles

Barthel et al (2011)

In a retrospective cohort study by Barthel et al (2011), patients with esophageal adenocarcinoma (EAC), who had undergone definitive chemoradiation therapy followed by cryotherapy for persistent BE, at a single center between 2004 and 2009, were identified from radiation and oncology treatment records. Patients were included in the study if they achieved a complete clinical response to chemoradiation, did not undergo esophagectomy, and received cryotherapy for persistent BE. Chemotherapy and radiation therapy were undertaken concurrently in all patients, and a complete clinical response was defined as no positron emission tomography (PET) scan, endoscopic, or histologic evidence of tumor persisting after definitive chemoradiation therapy.

All cryotherapy treatment sessions were performed on an outpatient basis, using the CryoSpray Ablation System. In each session, between one and three segments were treated, and when required, surveillance biopsy specimens were taken at the end of the session. Patients underwent endoscopic assessment six to eight weeks after each treatment session. BE was defined as endoscopic detection of columnar epithelium proximal to the gastric folds containing histologic evidence of intestinal metaplasia. Additional cryotherapy treatments and biopsies were undertaken if esophageal columnar epithelium remained at assessment endoscopy, otherwise biopsy specimens were taken from the gastric aspect of the neosquamocolumnar junction, and cryotherapy was not performed. BE ablation was considered complete if histology was negative

for dysplasia. Outcomes of interest included the reduction in Prague classification and dysplasia status following cryotherapy, as well as complications reported at the telephone interview conducted 24 to 48 hours after treatment and at subsequent endoscopy.

A total of 14 patients (12 male and 2 female), with dysplastic BE (HGD in 10 patients and LGD in 4 patients), and a mean age of 73.4 years, were included in the study. Following complete clinical response of EAC to chemoradiation therapy, the median length of persistent BE was Prague classification C1M4 (C=circumferential extent, M=maximal extent). The median time from EAC radiation treatment to the first cryotherapy treatment session was 258 days (Interquartile range [IQR] 88-1254 days). Each patient received a median of one (range 1-5) cryotherapy treatment session, and a total of 21 treatment sessions were performed for the 14 patients in this cohort. The median time from cryotherapy treatment to the last surveillance endoscopy with biopsy was 217 days (IQR 85-328 days).

Greenwald et al (2010a)

Patients with esophageal carcinoma, who were treated with endoscopic spray cryotherapy at 10 centers between 2006 and 2009, were enrolled in a retrospective cohort study by Greenwald et al (2010a). Patients were included in the study if they had been diagnosed with esophageal AC or SCC, and had received one or more treatments with endoscopic spray cryotherapy for either curative or palliative purposes.

All cryotherapy treatment sessions were performed on an outpatient basis, using the CryoSpray Ablation System. In each session, between one and five sites in the esophagus were treated, and treatment sessions were repeated every four to six weeks. A complete response to treatment was defined as complete local tumor eradication, as determined by endoscopic appearance and histological confirmation of the lack of residual disease. Follow-up endoscopy with esophageal biopsy was conducted every three to six months after ablation was complete. Safety outcomes of interest included the rate of stricture, bleeding, chest pain requiring narcotics, hemorrhage, perforation and other serious adverse events. In the efficacy analysis, the primary outcome was complete eradication of all luminal cancer, confirmed by histological examination of biopsy specimens. The complete eradication of all intestinal metaplasia was a secondary efficacy outcome.

A total of 79 patients (64 male and 15 female), with esophageal carcinoma (AC in 74 patients and SCC in 5 patients), and a median age of 76 years (range 51-93 years), were included in the study. The tumor stage of patients included T1 (75.9%), T2 (20.3%), T3 (2.5%), and T4 (1.3%), and the mean tumor length was 4 cm (range 1-15 cm). Each patient received a median of three (range 1-25) cryotherapy treatment sessions, and a total of 332 treatment sessions were performed for the 79 patients in this cohort. Fifty-three patients (67.1%) had received previous treatment for esophageal cancer, including EMR, concurrent chemotherapy/external beam radiotherapy, and PDT. Concurrent therapy was employed in 18 patients (22.8%), and included EMR, external beam radiotherapy, APC, RFA, and esophagectomy. Of the 79 patients enrolled in the study, 49 had completed treatment at the time of data collection and were included in the efficacy analysis. All 79 patients were included in the safety analysis. The baseline characteristics of the safety and efficacy cohorts appeared similar; however, no statistical analyses were provided. The mean follow-up was 10.6 months (SD 8.4 months).

Greenwald et al (2010b)

In a study by Greenwald et al (2010b), patients with BE, BE with LGD, HGD or IMCA, esophageal cancer (T1 or T2 N0 M0, AC and SCC), or severe squamous dysplasia, were enrolled in prospective treatment protocols at four centers between 2005 and 2007. Patients with HGD and IMCA were considered inoperable based on medical conditions or refused esophagectomy. Patients with invasive cancer were considered inoperable based on medical conditions or refused esophagectomy, and had refused, failed, or were ineligible for systemic therapy including chemotherapy or radiation therapy.

All cryotherapy treatment sessions were performed on an outpatient basis, using the CryoSpray Ablation System. Treatment sessions were repeated every four to six weeks until the target lesion was ablated or had diminished in size (tumors). Histological assessment of the underlying lesion was undertaken in patients who completed cryotherapy and had at least one follow-up endoscopy with biopsy. Safety outcomes of interest included the rate of dysphagia, odynophagia, chest pain, abdominal pain, sore throat, irregular heartbeat, or other symptoms, reported at the telephone or face-to-face interview following each treatment session. In the efficacy analysis, the main outcome of interest was the rate of complete response for HGD, all dysplasia, intestinal metaplasia, and cancer.

A total of 77 patients (57 male and 20 female) with a mean age of 69 years (range 36-93 years), were included in the study. Seven patients (9.1%) had BE, 45 patients (58.4%) had BE with HGD, 13 patients (16.9%) had BE with IMCA, 10 patients (13%) had esophageal cancer, and two patients (2.6%) had severe esophageal squamous dysplasia. The mean length of esophagus treated was 4 cm (SD 3.6 cm). Each patient received a median of four (range 1-10) cryotherapy treatment sessions, and a total of 323 treatment sessions were performed for this cohort of 77 patients. Of the 77 patients enrolled in the study, 72 were included in the efficacy analysis; however, only 24 patients had completed treatment at the time of data collection. All 77 patients were included in the safety analysis. The mean follow-up was 9.9 months (range 2-20 months), 13.8 months (range 10-18 months), and 9.3 months (range 3-13 months), for the HGD, IMCA, and stage I esophageal cancer groups, respectively.

Shaheen et al (2010)

Shaheen et al (2010) performed a retrospective analysis of patients with BE with HGD who were treated with endoscopic spray cryotherapy at nine centers between 2007 and 2009. Patients were included in the study if they had unifocal or multifocal HGD of any length. Previous endoscopic therapy was permitted if the results showed no evidence of residual AC, and residual HGD was present in the tubular esophagus at the initiation of cryotherapy treatment.

All cryotherapy treatment sessions were performed on an outpatient basis, using the CryoSpray Ablation System. In each session, between three and five sites in the esophagus were treated, and treatment sessions were repeated every two to three months until eradication of BE was confirmed by both histological and endoscopic findings. Safety outcomes of interest included the rate of perforation, stricture requiring dilation, bleeding requiring transfusion, and pain requiring narcotic analgesia or hospitalization. In the efficacy analysis, the main outcomes of interest included progression to esophageal AC, continued presence of HGD, complete eradication of HGD with persistent LGD, eradication of all dysplasia with persistent nondysplastic intestinal metaplasia, and eradication of all intestinal metaplasia.

A total of 98 patients (81 male and 17 female), with a mean age of 65 years (range 43-85 years), were included in the study. The mean length of BE at baseline was 5.3 cm (range 1-13 cm). A total of 333 treatment sessions were performed for the 98 patients in this cohort. Thirty-nine patients (39.8%) had received previous treatment, including EMR, Nissen fundoplication, APC, RFA, PTD, and partial esophagectomy. Of the 98 patients enrolled in the study, 60 had completed treatment at the time of data collection and were included in the efficacy analysis. Each of these 60 patients received a mean of four (SD 2.9) cryotherapy treatment sessions. All 98 patients were included in the safety analysis. The baseline characteristics of the safety and efficacy cohorts appeared similar; however, no statistical analyses were provided. The mean follow-up was 10.5 months (SD 8.3 months).

Dumot et al (2009)

In the study by Dumot et al (2009), high-risk patients with BE-associated HGD or IMCA were treated with endoscopic spray cryotherapy at a single center between 2005 and 2008. Patients were included in the study if they were deemed high-risk for esophagectomy based on specific medical conditions, or if they refused surgical intervention. Patients were excluded from the study if they were pregnant, less than 18 years of age, unable to give informed consent, or if they had a life expectancy of less than six months.

All cryotherapy treatment sessions were performed using the CryoSpray Ablation System. In each session, between three and six sites in the esophagus were treated, and treatment was repeated every six weeks. Treatment continued until complete ablation of Barrett's mucosa was achieved. Follow-up surveillance endoscopy with biopsy was performed at three month intervals for 12 months, then six month intervals for 12 months, then yearly. Safety outcomes of interest included the rate of immediate complications such as dysphagia, chest pain, odynophagia, and nausea and vomiting, which were assessed by telephone interview the day after treatment. In the efficacy analysis, the primary outcome of interest was the histological response which was defined by the worst pathology obtained at any level of the esophagus or gastric cardia in one of three categories: (1) incremental = absence of HGD and IMCA in all biopsy specimens, (2) partial = residual IMCA with absence of any dysplasia, and (3) complete = absence of any intestinal metaplasia or dysplasia.

Of the 39 patients originally enrolled in the study, a total of 37 patients received cryotherapy treatment. Five patients with invasive disease and one patient with squamous cell cancer were excluded from the analysis. Another patient was excluded because he was lost to follow-up immediately after completion of treatment. Safety and efficacy results were presented for the remaining 30 patients (21 male and 9 female), with HGD (25 patients) and IMCA (5 patients), and a mean age of 69.7 years (SD 11 years). The BE length at baseline was 6.1 cm (SD 4.1 cm). Eight patients (26.7%) had received previous therapy, including APC, PDT, and EMR. Each patient received a median of five (IQR 3-7) cryotherapy treatment sessions. The median follow-up was 12 months (IQR 6-24 months).

Johnston et al (2005)

Patients with a long-standing history of BE who were followed in a BE registry, were enrolled in a prospective pilot study by Johnston et al (2005). The level of dysplasia in these patients ranged from no history of dysplasia to multifocal HGD in a 6 cm segment of BE.

All cryotherapy treatment sessions were performed on an outpatient basis, using the CryoSpray Ablation System. Treatment sessions were repeated every four weeks, until complete endoscopic and histological reversal of BE was achieved. Follow-up endoscopy with esophageal biopsy was performed every four weeks following cryotherapy treatment. Safety outcomes, including complications, were assessed by telephone interview one week after treatment. In the efficacy analysis, the primary outcomes of interest were endoscopic and histologic reversal of BE. Complete endoscopic reversal was defined as no endoscopic evidence of residual columnar-appearing epithelium at the time of endoscopy. Complete histologic reversal was defined as no specialized intestinal metaplasia (SIM) in any of the post treatment surveillance biopsies, including the absence of subsquamous SIM.

A total of 11 male patients, with BE and a mean age of 59 years, were included in the study. The mean BE length at baseline was 4.6 cm (range 1-8 cm). Of the 11 patients enrolled, nine completed the treatment protocol and were included in the efficacy analysis. Two patients failed to complete the study, one due to a large hiatal hernia which precluded the ability to completely eradicate his BE, and the other due to severe arthritis predating study enrollment. All 11 patients were included in the safety analysis. In the nine patients who completed the treatment protocol, the mean number of cryotherapy treatment sessions was 3.6 (range 1-6). The mean follow-up was 12 months (range 6-20 months).

Critical appraisal

The published evidence available for inclusion in this report was limited to six case series studies, half of which had a retrospective design (Barthel et al 2011; Greenwald et al 2010a; Shaheen et al 2010). It has been suggested that the effect of ablative treatment modalities such as cryotherapy can be exaggerated in observational studies, due to a number of factors, including spontaneous regression, sampling error, and variability of histological interpretation of biopsy specimens (Shaheen et al 2010). In general, the sample sizes of included studies were small, ranging from 11 to 98 patients. In several studies, the efficacy analysis was based on a subset of the enrolled patient population, as not all patients had completed the cryotherapy treatment protocol at the time of publication. It is also likely that there is patient overlap between several studies, which were conducted at the same centers. The length of follow-up in most studies was limited to 12 months or less, and as such it was not possible to assess the long-term safety and efficacy of cryotherapy. The study limitations outlined above were generally acknowledged by the authors of most studies.

Inclusion criteria were reported in all six included studies and were generally limited; however, exclusion criteria were only reported in two studies (Barthel et al 2011; Dumot et al 2009). All six studies provided detailed information regarding the cryotherapy treatment protocols used; however, cryotherapy dosimetry, including freeze time, thaw time, and the number of freeze-thaw cycles, varied among patients in three of the studies (Barthel et al 2011; Greenwald et al 2010b; Dumot et al 2009). In two of the studies (Greenwald et al 2010b; Dumot et al 2009), cryotherapy dosimetry was altered part of the way through the study, and this may have affected the outcomes of cases treated in the earlier part of the study, compared with those treated in the later part of the study. A number of studies reported that some patients had undergone treatment with endoscopic or systemic therapies prior to cryotherapy, while some patients were undergoing

other treatments at the same time as cryotherapy, making it difficult to assess the true effect of cryotherapy treatment in these patients.

Two studies reported that the trial was supported by CSA Medical Inc, the manufacturer of the CryoSpray Ablation System, through a grant for statistical analysis and by assisting in data collection at some sites; however, the company did not play any role in trial design or analysis, interpretation of the data, or in writing the report (Greenwald et al 2010a; Greenwald et al 2010b). Another study reported that the trial was funded in part by a grant from CSA Medical Inc, but did not specify which elements of the trial this funding assisted with (Shaheen et al 2010). Three studies did not explicitly state the source of trial funding (Barthel et al 2011; Dumot et al 2009; Johnston et al 2005). Barthel et al (2011) reported that all authors disclosed no financial relationships that were relevant to the publication. In five studies, one or more authors disclosed financial relationships that were relevant to the publication, including membership of the CSA Medical Inc advisory committee, receipt of research grants or other research support from the company, as well as consultant roles with the company (Greenwald et al 2010a; Greenwald et al 2010b; Shaheen et al 2010; Dumot et al 2009; Johnston et al 2005). Johnston et al (2005) reported that the primary author was the inventor of the CryoSpray Ablation System, but had permanently divested himself of all potential future royalties; although he did serve as a consultant to CryMed Technologies Inc (now known as CSA Medical Inc).

Safety and efficacy

Safety

In the study by Barthel et al (2011), 12 patients (85.7%) reported no complaints, including no cases of chest pain, hematemesis indicating bleeding, or treatment-related dysphagia, at the postprocedure telephone survey 24 hours after cryotherapy. Two patients (14.3%) complained of a sore throat, but did not require narcotic therapy or urgent evaluation by a physician, and were managed conservatively with oral menthol lozenges. These cases of sore throat occurred following two of the 21 (9.5%) treatment sessions. No cases of interval complications or esophageal strictures were identified at the subsequent surveillance endoscopy. No major complications were experienced by any patients in this cohort.

Greenwald et al (2010a) reported that no serious adverse events, including perforation and hemorrhage, occurred in any of the 79 patients (who underwent 332 treatment sessions) in the study (Table 4). Benign stricture was observed in 12.7% of patients; however, all of these patients had received previous tumor therapy, and five of these patients received additional endoscopic therapy during or after cryotherapy treatment (Table 4). Of the 10 patients who developed a benign stricture, nine demonstrated narrowing of the esophageal lumen prior to the initiation of cryotherapy treatment. Post-treatment pain requiring the use of narcotic analgesics was reported in 25.3% of patients (Table 4). Eight patients (10.1%) died of disease during the study period, including two patients who were T1 (T1a-1, T1b-1), five patients who were T2 and one patient who was T3. Each of the eight patients had undergone previous treatments, including PDT (1 patient), radiation (2 patients), concurrent chemoradiation (4 patients), or PDT and chemoradiation (1 patient). These patients received between two and 12 cryotherapy treatment sessions and survived up to 12 months after cryotherapy was stopped.

Table 4: Adverse events following endoscopic cryotherapy (Greenwald et al 2010a)

Adverse event	Number of patients (%)
Benign stricture*#	10 (12.7)
Post-treatment pain requiring narcotic analgesia	20 (25.3)
Perforation	0 (0)
Hemorrhage	0 (0)

*All 10 patients had received previous tumor therapy, including endoscopic resection (5 patients), external beam radiation therapy (2 patients), photodynamic therapy (PDT) alone (1 patient), PDT and endoscopic resection (1 patient), and concurrent chemotherapy and external beam radiation therapy (1 patient).

#Five of these 10 patients received additional endoscopic therapy during or after cryotherapy treatment, including endoscopic resection (3 patients), endoscopic resection and argon plasma coagulation (APC) (1 patient) and APC alone (1 patient).

Greenwald et al (2010b) reported that overall, cryotherapy was well tolerated, with no side effects or complications reported in 155 procedures (48%). Where reported, side effects were generally mild in severity (Table 5). Commonly reported side effects included chest pain (17.6%), dysphagia (13.3%) and odynophagia (12.1%) (Table 5). A total of 22 patients (28.6%) reported no side effects or complications during their entire treatment. Patients were more likely to experience side effects when the treated esophagus length was greater than 6 cm ($P=0.0105$); however, no significant differences in symptom frequency or severity were observed based on diagnosis ($P=0.63$), gender ($P=0.91$) or age (less than 65 years compared with 65 years and over) ($P=0.49$). Serious adverse events related to treatment were reported in two patients (2.6%). One case of gastric perforation (1.3%) occurred in a patient with Marfan syndrome, and laparotomy revealed a perforation in the posterior wall of the stomach, not at the cryotherapy treatment site. Another patient developed a lip ulcer (1.3%), as a result of cold injury from contact with the endoscope, which resolved in four days without specific treatment. Minor adverse events related to treatment were reported in three patients (3.9%). All three, with Barrett's HGD from 6 to 12 cm in length, had esophageal stricture that responded to balloon dilation therapy.

Table 5: Number and duration of side effects following endoscopic cryotherapy (Greenwald et al 2010b)

Side effect	None	Mild	Moderate	Severe	Duration* (days)
	Number of side effects (%)				
Chest pain	266 (82.4)	45 (13.9)	10 (3.1)	2 (0.6)	3.7 ± 2.0
Dysphagia	280 (86.7)	24 (7.4)	19 (5.9)	0 (0)	4.9 ± 2.4
Odynophagia	284 (87.9)	27 (8.4)	11 (3.4)	1 (0.3)	4.5 ± 2.5
Sore throat	292 (90.4)	29 (9.0)	1 (0.3)	1 (0.3)	1.9 ± 1.0
Nausea	307 (95.0)	16 (5.0)	0 (0)	0 (0)	2.2 ± 1.2
Abdominal pain	309 (95.7)	10 (3.1)	1 (0.3)	3 (0.9)	2.7 ± 1.8
Irregular heartbeat	315 (97.5)	8 (2.5)	0 (0)	0 (0)	NR
Fever	320 (99.1)	3 (0.9)	0 (0)	0 (0)	1.7 ± 1.1

NR: not reported

*Data presented as mean ± standard deviation. Information on symptom duration was available for 100 procedures where patients were contacted seven days after the procedure, including 34 procedures for chest pain, 18 procedures for dysphagia, 12 procedures for odynophagia, 11 procedures for abdominal pain, 9 procedures for sore throat, 4 procedures for nausea/vomiting and 3 procedures for fever.

The study by Shaheen et al (2010) reported no serious adverse events, including perforations, in any patients. Strictures were reported in three patients (3.1% of patients and 0.9% of treatment sessions), and all were successfully treated with endoscopic dilation (requiring 2, 3, and 3 dilations respectively). Severe chest pain was reported in two patients (2% of patients and 0.6% of treatment sessions), and both were successfully treated with oral narcotics on an outpatient basis. One patient was hospitalized for bright red blood per rectum (1% of patients and 0.3% of treatment sessions) following treatment, and was observed overnight. No significant changes in hematocrit were noted, and no other assessments of the patient were performed.

Disease progression occurred in one patient (1% of patients and 0.3% of treatment sessions), despite treatment with cryotherapy (Shaheen et al 2010). A nodule at the gastro-esophageal junction was observed in this patient at the second planned cryotherapy treatment session, and as a result EMR was performed. Pathology results indicated an intramucosal AC, which was then successfully treated with esophagectomy, and the patient remained cancer free one year later.

Minor adverse events reported by Dumot et al (2009) included mild chest pain (heartburn-like sensation) in at least one treatment session (23.3%), severe pain lasting up to seven days (10%), mild to moderate stricture in the location of previous narrowing from peptic strictures or endoscopic therapy (10%), and a lip ulcer caused by accidental contact with the cold endoscope (3.3%) (Table 6). Severe pain lasting up to seven days was resolved with a short course of narcotic analgesics, and all patients suffering from stricture required endoscopic dilation. The only major adverse event reported in this study was one case of gastric perforation (3.3%), which occurred in a patient with Marfan syndrome, and was caused by overdilatation of the stomach (Table 6). This patient underwent laparotomy and was being followed expectantly, with serial surveillance revealing focal HGD. Of the 37 patients originally enrolled in the study who were treated with cryotherapy, 36 patients (97.3%) resumed their normal activity and diet the day after treatment.

Table 6: Adverse events following endoscopic cryotherapy (Dumot et al 2009)

Adverse event	Number of patients (%)
Mild chest pain	7 (23.3)
Severe pain lasting up to 7 days	3 (10)
Mild to moderate stricture	3 (10)
Lip ulcer	1 (3.3)
Gastric perforation	1 (3.3)

Johnston et al (2005) reported that there were no complications, including significant bleeding, esophageal stricture or perforation, following cryotherapy. In addition, post cryotherapy surveillance biopsy specimens taken at either one or six months' follow-up, revealed no cases of dysplasia. Two patients suffered from esophageal ulcers following cryotherapy, which required treatment to be delayed until the ulcers had healed. In both patients the ulcers healed and cryotherapy was resumed. The authors did not suggest that these ulcers were related to cryotherapy treatment. Two patients (18.2% of patients and 4.3% of treatment sessions) reported symptoms following cryotherapy. One patient reported chest discomfort and the other reported mild solid-food dysphagia, both on postprocedure day one. Only one of these patients required analgesia for their symptoms, and both patients had resolution of symptoms within 48 hours.

Efficacy

Barthel et al (2011) reported that following cryotherapy treatment, significant reductions in median circumferential and maximal Prague criteria, and a histological downgrading of dysplasia, were observed in all 14 patients. Specifically, the median length of persistent BE was reduced from Prague classification C1M4 (C=circumferential extent, M=maximal extent) after chemoradiation at baseline, to C0M1 following cryotherapy treatment ($P=0.009$ with respect to circumferential extent and $P=0.004$ with respect to maximal extent of BE). Of the 10 patients with HGD after chemoradiation at baseline, two (20%) were reduced to LGD, six (60%) were reduced to BE with no dysplasia, and two (20%) were reduced to no BE, following cryotherapy treatment. Of the four patients with LGD at baseline, three (75%) were reduced to BE with no dysplasia, and one (25%)

was reduced to no BE, following cryotherapy treatment. The median time from cryotherapy to the last surveillance endoscopy with biopsy was 217 days (IQR 85-328 days).

In the study by Greenwald et al (2010a), of the 49 patients who had completed the cryotherapy treatment protocol at the time of data collection, 61.2% demonstrated a complete response for luminal disease, at a mean follow-up of 10.6 months (SD 8.4 months) (Table 7). Final histology following successful treatment included normal squamous mucosa in 16 patients (53.3%), intestinal metaplasia in nine patients (30%), LGD in four patients (13.3%), and HGD in one patient (3.3%). The median number of cryotherapy treatment sessions in the complete response group (3, range 1-13) appeared similar to that of the treatment failure group (3, range 1-12); however, no statistical analyses were provided. No significant difference was observed between the complete response and treatment failure groups with regard to age, tumor length, or number of subjects receiving previous or concurrent therapy; however, no statistical analyses were provided. In this cohort of 49 patients, a total of eight patients (16.3%) received other therapies while undergoing cryotherapy. In the complete response group, concurrent treatments included EMR/APC (1 patient), EMR alone (1 patient), and RFA (1 patient). In the treatment failure group, concurrent therapies included esophagectomy (4 patients) and APC (1 patient). If patients who received concurrent treatments were excluded from the efficacy analysis, a complete response for luminal disease was observed in 65.9% (27/41) of patients.

The majority of patients in this cohort had T1 tumors (73.5%), with 72.2% demonstrating a complete response for luminal disease, at a mean follow-up of 11.5 months (SD 2.8 months) (Table 7) (Greenwald et al 2010a). Most T1 tumors were mucosal (T1a), with 75% demonstrating endoscopic remission (Table 7).

Table 7: Response to treatment with endoscopic cryotherapy by tumor status (Greenwald et al 2010a)

	Complete endoscopic response	Persistent tumor
	Number of patients (%)	
Total	30 (61.2)	19 (38.8)
By tumor stage		
T1	26 (72.2)	10 (27.8)
<i>Mucosal</i>	18 (75)	6 (25)
<i>Submucosal</i>	6 (60)	4 (40)
<i>Not stated</i>	2 (100)	0 (0)
T2	3 (30)	7 (70)
T3	1 (50)	1 (50)
T4	0 (0)	1 (100)

Greenwald et al (2010b) reported that of the 77 patients included in the efficacy analysis, 24 had completed the cryotherapy treatment protocol at the time of data collection, including 17 with HGD, four with IMCA, and three with stage I esophageal AC. In patients with HGD, the rates of complete response of HGD, dysplasia, and intestinal metaplasia were 94%, 88% and 53%, respectively at a mean follow-up of 9.9 months (range 2-20 months) (Table 8). In patients with IMCA, the rates of complete response of cancer, HGD, dysplasia, and intestinal metaplasia were 100%, 100%, 100%, and 75%, respectively at a mean follow-up of 13.8 months (range 10-18 months) (Table 8). In patients with stage I esophageal cancer, the rates of complete response of

cancer, HGD, dysplasia, and intestinal metaplasia were 100%, 100%, 100%, and 67%, respectively at a mean follow-up of 9.3 months (range 3-13 months) (Table 8).

Table 8: Response to treatment with endoscopic cryotherapy (Greenwald et al 2010b)

	Barrett's HGD	Barrett's IMCA	Barrett's carcinoma
	Number of patients (%)		
Complete response – cancer	-	4 (100)	3 (100)
Complete response – HGD	16 (94)	4 (100)	3 (100)
Complete response – dysplasia	15 (88)	4 (100)	3 (100)
Complete response – intestinal metaplasia	9 (53)	3 (75)	2 (67)

HGD: high grade dysplasia
IMCA: intramucosal carcinoma

Shaheen et al (2010) reported that of the 98 patients included in the efficacy analysis, 60 had completed the cryotherapy treatment protocol at the time of data collection. Of these 60 patients, 58 (96.7%) had complete eradication of HGD, 52 (86.7%) had complete eradication of intestinal dysplasia, and 34 (56.7%) had complete eradication of intestinal metaplasia, at a mean follow-up of 10.5 months (SD 8.3 months). Biopsy specimens revealed subsquamous BE in two patients (3.3%).

Dumot et al (2009) reported that of the 30 patients that completed cryotherapy, 27 (90%) demonstrated a downgrading of pathology stage following treatment. Specifically, a complete response to treatment was confirmed in 23 (92%) patients with HGD and four (80%) patients with IMCA. At last follow-up, 22 patients were alive and free of cancer, with complete responses persisting in 18 patients (72%) with HGD and four patients (80%) with IMCA. The median length of follow-up was 12 months (IQR 6-24 months).

In the study by Johnston et al (2005), a total of 11 patients received treatment with cryotherapy; however, only nine completed the cryotherapy treatment protocol. Endoscopic reversal of BE was demonstrated in all nine patients (100%); however, at the one-month follow-up surveillance endoscopy, two patients (22.2%) developed fragments of SIM distal to the squamo-columnar junction. Therefore, histological reversal of BE was demonstrated in seven patients (77.8%). At the six-month follow-up surveillance endoscopy, no subsquamous SIM was observed in any patients. The mean follow-up for this cohort of patients was 12 months (range 6-20 months).

Cost impact

No studies assessing the cost-effectiveness of cryotherapy for the treatment of BE or esophageal cancer were identified.

A study by Johnston et al (1999) suggested that the cost of this type of cryotherapy compared with other ablative modalities remained to be determined, although given that cryotherapy devices are technically simple in design, their projected cost should be considerably less than the cost of devices required for PDT, APC, laser photoablation, or electrocautery. In addition, cryotherapy devices are reusable and represent a one-time purchase, and cryotherapy catheters while disposable, should be relatively inexpensive and compare favorably in price to MPEC catheters (Johnston et al 1999).

A more recent report by the American Society for Gastrointestinal Endoscopy (Rodriguez et al 2008) listed the costs associated with the two main commercially available devices for endoscopic spray cryotherapy in the gastrointestinal tract (Table 9).

Table 9: Cost of endoscopic spray cryotherapy devices (Rodriguez et al 2008)

Product	Manufacturer	Special features	Generator price (\$USD)	Probe price (\$USD)
CryoSpray Ablation System	CSA Medical Inc (Baltimore, Maryland, US)	Liquid nitrogen	\$39,500	\$845 for each CryoSpray Ablation
Polar Wand Cryotherapy System	GI Supply division of Chek-Med Systems Inc (Camp Hill, Pennsylvania, US)	Pressurized CO ₂ ; side-port catheters available	\$9,000	\$625 for 5 catheters; \$900 for 5 side-port catheters

USD: US dollars

Clinical practice guidelines and consensus statements

The American Gastroenterological Association has developed a medical position statement on the management of BE, including the use of cryotherapy (Spechler et al 2011). The key recommendations within this guideline are outlined below.

The role of endoscopic therapy in patients with BE

- Current endoscopic techniques used to eradicate BE include RFA, PDT, cryotherapy, thermal energy application, and EMR. The most commonly used technologies currently are RFA and EMR used alone or in combination. Evidence for their efficacy has emerged rapidly over the past decade.
- The goal of endoscopic eradication therapy is the elimination of all Barrett's epithelium to prevent neoplastic progression. Complete eradication appears to be more effective than therapy that removes only a localized area of dysplasia in Barrett's epithelium.
- Although RFA and PDT have not been compared head-to-head in controlled trials, RFA appears to have at least comparable efficacy and fewer serious adverse effects compared with PDT.
- The second goal of eradication therapy is to achieve reversion to normal-appearing squamous epithelium within the entire length of the esophagus without islands of buried intestinal metaplasia. RFA can lead to reversion of the metaplastic mucosa to normal-appearing squamous epithelium in a high proportion of subjects at any stage of BE. The data to date show that reversion to squamous epithelium can persist for up to 5 years.
- There are no data from controlled trials showing that endoscopic eradication therapy, including RFA and cryotherapy, is more effective at reducing cancer risk or more cost-effective than long-term endoscopic surveillance in patients with BE in the absence of dysplasia (non-dysplastic Barrett's metaplasia).
- RFA therapy for patients with LGD leads to reversion to normal-appearing squamous epithelium in >90% of cases.
- RFA therapy for patients with HGD reduces progression to esophageal cancer, as shown in a randomized sham-controlled trial. Several additional uncontrolled trials have shown a similar reduction in cancer development and sustained reversion to squamous mucosa in a large percentage of patients.
- The current literature is inadequate to assess the ability of cryotherapy to achieve sustained reversion of the metaplastic mucosa to normal-appearing squamous epithelium in subjects at any stage of BE. Further longitudinal studies are needed.
- EMR is both a valuable diagnostic/staging procedure and a potentially therapeutic procedure that should be performed in patients who have dysplasia associated with visible mucosal irregularities in BE.

The role of esophagectomy

- Most patients with HGD (70%–80%) can be successfully treated with endoscopic eradication therapy. Esophagectomy in patients with HGD is an alternative; however, current evidence suggests that there is less morbidity with ablative therapy.
- Before proceeding with esophagectomy, patients with HGD or IMCA with BE should be referred for evaluation by surgical centers that specialize in the treatment of foregut cancers and HGD.

Training and education impact

No information was identified that detailed the training and education requirements for clinicians wishing to add cryotherapy for the treatment of BE and esophageal cancer to their repertoire. The United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) has published a clinical guidance document on ablative therapy for the treatment of BE (NICE 2010). While cryotherapy was not one of the ablative therapies assessed in this document, it was recommended that all treatments for HGD and intramucosal cancer in BE should be performed by specialist esophago-gastric cancer teams with the appropriate experience and facilities (NICE 2010).

Summary

The cause of esophageal cancer is unknown; however, BE is one of the major risk factors associated with the development of this type of cancer. Esophagectomy is the gold-standard treatment for curing early stage esophageal cancer; however, the morbidity rate associated with this procedure remains high. This has stimulated the development of newer endoscopic treatments, including ablation and mucosal resection, which preserve the esophagus.

Cryotherapy is one of the most recent ablation techniques that has been used in the management of BE and esophageal cancer. This technique employs cycles of rapid freezing and slow thawing, using liquid nitrogen or carbon dioxide gas to destroy tissues through immediate and delayed effects. The two main commercially available devices for endoscopic spray cryotherapy in the gastrointestinal tract are the CryoSpray Ablation System and the Polar Wand Cryotherapy System.

Searches failed to identify any RCTs or non-randomized comparative studies comparing cryotherapy with other ablative modalities for the treatment of BE and/or esophageal cancer. A total of six case series studies that assessed the safety and efficacy of endoscopic spray cryotherapy were selected for inclusion in this report. All studies used the CryoSpray Ablation System.

- Safety outcomes were reported in all six studies. The rate of complications was generally low. Commonly reported minor complications included chest pain, sore throat and dysphagia. Major complications, including perforation and hemorrhage, were rare; however, esophageal stricture was reported in four of the six studies. One study reported that eight patients (10.1%) died of esophageal cancer during the study period; however, these patients survived up to 12 months after cryotherapy was stopped, and all had previously undergone other forms of treatment, including PDT, radiation, and chemoradiation. As such, it is unlikely that these deaths were related to cryotherapy treatment.
- The results from these studies suggest that endoscopic spray cryotherapy is effective in treating patients with Barrett's HGD and early esophageal cancer, including those who have failed other forms of treatment, at least in the short-term. Specifically, cryotherapy treatment was associated with a complete eradication of Barrett's HGD in 72-100% of patients. For patients suffering from early stage esophageal cancer, a complete response to cryotherapy treatment was observed in 61-100% of patients.

The ability to draw firm conclusions about the safety and efficacy of this technology was limited by a number of factors. Firstly, the sample sizes of the included studies were generally small, ranging from 11 to 98 patients. In a number of the studies, not all patients had completed all planned cryotherapy treatments at the time of publication, and the efficacy analysis was based on a subset of the enrolled patient population. It is also likely that there is patient overlap between several studies, which were conducted at the same centers. Secondly, none of the studies in the report were able to assess the long-term safety and efficacy of cryotherapy, as the length of follow-up was limited to 12 months or less in the majority of studies. Finally, the retrospective design of some studies may have increased their risk of selection bias.

Recommendations

Based on the limited case series evidence presented in this report, endoscopic spray cryotherapy appears to be a safe and effective treatment for patients suffering from BE with HGD, or early esophageal cancer. The procedure was effective in eradicating disease in a considerable proportion of these patients, including those who had failed other forms of treatment. Cryotherapy was well tolerated by patients and was associated with a low rate of serious complications. However, further prospective studies with larger sample sizes, longer follow-up periods, and which compare cryotherapy to other ablative modalities, are needed in order to confirm the safety and efficacy of the procedure.

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Appendix A

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention ¹	Diagnostic accuracy ²	Prognosis	Aetiology ³	Screening Intervention
I ⁴	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among consecutive persons with a defined clinical presentation ⁶	A prospective cohort study ⁷	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among non-consecutive persons with a defined clinical presentation ⁶	All or none ⁸	All or none ³	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial⁹ ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study¹⁰ ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study ⁶	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ¹¹	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.