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Role of Liquid Nitrogen Spray Cryotherapy in Dysphagia Management for Esophageal Cancer

This report summarizes a multidisciplinary session focused on the potential of spray cryotherapy (SCT) in managing dysphagia associated with esophageal cancer. The session convened key opinion leaders (KOLs) from oncology, gastroenterology, and related fields to examine the therapy's current applications, operational best practices, and future directions.

Clinical Practice Model Development

KOL Team Members

- Neil Sharma MD: Enow Project Coordinator (GI – Interventional Endoscopist)
- Toufic Kachaamy MD: City of Hope (GI - Interventional Endoscopist)
- Shivangi Kothari MD: University of Rochester (GI - Interventional Endoscopist)
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- Ravneet Bajwa MD: McLeod Health (Medical Oncology)
- Madappa Kundrada MD: Banner Health (Medical Oncology)

CPM Development Process

The KOLs have worked on reviewing current literature. This was followed by a session to discuss their findings and perspectives. There was a robust dialogue including discussion of the National Comprehensive Cancer Network (NCCN) guidelines, personal experiences and debate on the literature with a goal of creating a consensus on recommendations for a practical and clinically relevant practice model in the KOL session.

The session was designed to:

1. Evaluate Current Utilization: Review clinical scenarios where SCT is employed, assess its efficacy, and compare it to conventional modalities like stents and radiation therapy.
2. Establish Operational Best Practices: Develop protocols for patient selection, timing, and procedural safety.
3. Chart a Future Roadmap: Identify research gaps, areas for innovation, and opportunities for collaboration to optimize SCT in clinical settings.

The discussions emphasized fostering multidisciplinary collaboration and leveraging diverse perspectives to develop a comprehensive understanding of SCT's role in dysphagia management. This subsequently led to the creation of the proposed clinical practice model (CPM).

The Current Landscape of Dysphagia Management

Dysphagia is a prevalent and distressing symptom in esophageal cancer and has been recognized by American Society of Clinical Oncology (ASCO), American College of Gastroenterology (ACG), and Palliative care literature as the most significant factor impacting quality of life in patients with esophageal cancer.

Traditionally dysphagia secondary to esophageal cancer is managed with esophageal stents or radiotherapy. Balloon dilation alone has limited efficacy in the setting of luminal malignancy and is not typically recommended.

While these interventions (stents and radiation) effectively palliate dysphagia, they have significant limitations.

Esophageal Stents

- Prone to complications such as tissue ingrowth, food bolus impaction, and biggest risk of stent migration which can be mitigated to some extent with suturing the stent in place. Catastrophic bleeding and perforation have been reported as well.
- Patients can experience side effects such as discomfort, chest pain, and reflux.
- Patients with extended survival due to advancements in systemic therapies may require reintervention.

Radiation Therapy

- Effective but slow to provide relief, taking weeks to improve symptoms. Poor choice for immediate palliation in severely symptomatic patients.
- Causes esophagitis and inflammation, which can exacerbate dysphagia initially.
- Often patients may have had radiation with neoadjuvant therapy as well, thereby limiting the amount of radiation they can receive in the future for residual/recurrent disease causing dysphagia.

PEG Tube

- Feeding tubes can play a significant role in management of esophageal cancer by helping patients maintain nutritional status.
- However, patient QOL remains severely reduced as feeding tubes do not directly address dysphagia and patients must continue to limit oral intake.
- Additionally, gastrostomy tubes have the potential to cause abdominal wall tumor seeding, compromise gastric conduit formation, infection, and to become dislodged.

Liquid Nitrogen Spray Cryotherapy (LNSCT)

LNSCT offers a novel, non-invasive approach to dysphagia management:

Tumor Ablation

Reduces tumor bulk without mechanical disruption

Patient Tolerability

Fewer adverse effects compared to stents and radiotherapy

Rapid Symptom Relief

Facilitates faster improvement in swallowing compared to radiation therapy however not as fast as stent

Superior Freezing

LNSCT achieves lower freezing temperatures (-196 degrees Celsius) compared to balloon cryotherapy (-78 degrees Celsius) and has greater depth of penetration

LNSCT is referenced as an accepted modality to palliate dysphagia in the National Comprehensive Cancer Network (NCCN) Guidelines.

Comparative Evidence Overview

The following cards provide a detailed overview of the evidence supporting various treatment modalities for dysphagia, presenting key studies and their findings for each approach.

Evidence: Esophageal Stents

Authors	Year	Study Type	Key Take Home Points
Włodarczyk JR, Kużdżał J, Et al.	2018	Retrospective	Excellent for alleviating dysphagia with 12.4% recurrence. Low major adverse events. Minor adverse events: chest pain (54.5%), delayed complete stent expansion (12.0%), feeling of a foreign body (25.3%), hiccup (1.6%), gastroesophageal reflux (45.6%) and post-discharge pneumonia (2.5%). N- 442
Reijm AN, Didden P, Bruno MJ, Spaander MCW	2016	Prospective Single Site	Palliation of dysphagia within 24 hours. The rate of significant pain increased from 0% at baseline to 60% on Day 1 ($P < 0.001$), followed by 37% and 25% on Days 7 and 14, respectively. N- 997

Evidence: Radiation Therapy

Authors	Year	Study Type	Key Take Home Points
Ye M, Han D, Mao Z, Cheng G	2022	Prospective Single Site	Acute side effects include dysphagia and bone marrow suppression. Severe late side effects include fistula, radiation pneumonia, or even stenosis. N - 66
Das A, Kalita AK, Bhattacharyya M, Et al.	2023	Prospective Single Site	Dysphagia relief was observed in 82.45%. The median dysphagia score decreased from 3 to 2 at the end of the 3-month post-treatment. Radiation esophagitis in 26.31%. N -57

Evidence: Spray Cryotherapy Studies

Authors	Year	Study Type	Key Take Home Points
Eluri S, Kaul V, Sharma N Et al.	2019	Multicenter Prospective	SCT showed significant improvement in Quality of Life (34.9 to 29) & Dysphagia (1.9 to 1.3) in patients without concomitant use of chemotherapy, radiation or other interventions. (monotherapy study)
Shah T, Kushnir V, Mutha P, Et al.	2019	Multicenter Prospective Pilot Trial	SCT was applied in patients at time of presentation with dysphagia and was safe to use in combination with chemotherapy and radiation in a neoadjuvant approach. Improved dysphagia in a neoadjuvant approach in combination with chemotherapy and radiation. N - 21
Kachaamy T, Sharma N, Pannala R Et al.	2020	Multicenter Prospective	SCT can be performed safely in conjunction with standard of care chemotherapy. SCT cane be performed in patients who have had prior radiation therapy. No dose limitations noted, and shorter intervals between therapy showed significant improvements in dysphagia. N – 24, 71 procedures

Evidence: Early Cryotherapy Studies (2019-2020)

Authors	Year	Study Type	Key Take Home Points
Eluri S, Kaul V, Sharma N Et al.	2019	Multicenter Prospective	SCT showed significant improvement in Quality of Life (34.9 to 29) & Dysphagia (1.9 to 1.3) in patients without concomitant use of chemotherapy, radiation or other interventions. (monotherapy study)
Shah T, Kushnir V, Mutha P, Et al.	2019	Multicenter Prospective Pilot Trial	SCT was applied in patients at time of presentation with dysphagia and was safe to use in combination with chemotherapy and radiation in a neoadjuvant approach. Improved dysphagia in a neoadjuvant approach in combination with chemotherapy and radiation. N - 21
Kachaamy T, Sharma N, Pannala R Et al.	2020	Multicenter Prospective	SCT can be performed safely in conjunction with standard of care chemotherapy. SCT cane be performed in patients who have had prior radiation therapy. No dose limitations noted, and shorter intervals between therapy showed significant improvements in dysphagia. N – 24, 71 procedures

Evidence: Recent Cryotherapy Studies

Authors	Year	Study Type	Key Take Home Points
Handa Y, Leggett CL, Iyer PG et al.	2022	Prospective Single Site	Most patients who underwent SCT were able to avoid esophageal stent placement & live without significant dysphagia. For those limited patients requiring stenting, they were able to be defer stenting for >1year. N 56, 199 procedures
Kachaamy T, Sharma N, Shah T, Et al.	2023	Multicenter Prospective	SCT is synergistic with standard of care chemotherapy. Significant improvements in dysphagia and quality of life in combination therapy. Trends showed potential for improved survival in patients with combination therapy. N – 55, 175 procedures

Timing and Integration with Systemic Therapies

1 Pre-Chemotherapy

Acts as a bridge for symptom palliation, improving swallowing and nutritional status before systemic therapy initiation.

With the advent of molecularly targeted therapies and need for biomarker testing/next gen sequencing tests prior to initiating systemic treatment, there is usually a delay of 1-2 weeks. This may be an ideal time where sequential cryotherapy prior to initiating systemic therapy can be considered.

2 During Chemotherapy

Best performed between cycles to reduce risks of bleeding and infection.

Avoid during nadir periods with low white blood cell or platelet counts to minimize complications.

If given concurrently, it will be ideal to give closer to upcoming cycle to mitigate risk of infection or bleeding during nadir blood counts.

3 With Radiotherapy

Pre-Radiation: Used to clear luminal obstructions, facilitating uniform radiation dose delivery. Can administer up to 48 hours prior to neoadjuvant radiation therapy.

During radiation: Likely safe to administer, but limited impact on quality of life during radiation therapy.

Post-Radiation: Typically delayed 6–8 weeks post-treatment to prevent exacerbation of esophagitis and allow healing.

LNSCT can be performed as an inpatient or outpatient while the patient awaits complete staging and work up without compromising definitive treatments. Since there is no significant down time post procedure, it is not expected to delay essential systemic treatment for the patient.

Note that biopsy to assess for residual disease that could be treated with spray cryotherapy should be delayed by 6 – 8 weeks after radiation to minimize likelihood of false positive (non-viable tumor cells). SCT would be initiated after radiation therapy in that time frame if biopsies are positive.

Procedural Insights and Best Practices

LNSCT uses a low-temperature cryogen to induce controlled tissue necrosis. Detailed procedure protocols are essential for safe and effective application.

Equipment Needed

Equipment	Manufacturer
Decompression Tube – 16Fr or 20 fr.	Steris
7Fr Spray catheter & introducer	Steris
Distal Cap	Olympus or Steris
50 or 60 cc syringe with nose compatible to endoscope	N/A
Standard upper endoscope (may need 5.4Fr Neonatal upper endoscope in some cases)	Olympus/Fuji

Protocol Highlights

- Plan spray application distal to proximal fashion for improved visualization
- Use a clear distal cap to improve visualization with standard upper endoscopes
- Standard protocol: three cycles of 30-second cryogen delivery to the tumor site
- Timer begins when the entire initial target area has been covered by frost
- Avoid use of water for lavage during the procedure
- Treatments are given every 1 to 4 weeks with slowly increasing time between treatments

Safety Protocols and Special Considerations

1

Safety Measures

High, consistent suction during the procedure to prevent cryogen retention is key. Decompression tube must be placed with 2 black lines just distal to the GEJ for adequate decompression. Placement and suction should be initiated prior to any cryoablation.

2

Contraindications

Inability to pass suction tube with confirmation of appropriate placement, high grade luminal obstruction preventing meaningful access to tumor, suspected or known perforation, and patients unfit for anesthesia.

3

Dilation with Cryoablation

Dilation post cryoablation has becoming increasingly adapted in patients with narrow lumen. Typically done with balloon catheter dilation only after cryoablation, and exercised with caution. Recommended to dilate approximately no more than 3mm above initial diameter in any given session.

For detailed technique demonstration, a video is available at: **https://www.youtube.com/watch?v=_He5vrSEqww&authuser=1**

Post-Procedure Care and Outcome Evaluation

Post-Procedure Recommendations

- Patients may continue with regular diet once fully recovered from anesthesia unless they have an extremely narrow diameter lumen (typically <8mm)
- Patients may resume regular activity post procedure along with routine medications
- Most patients will experience little to no pain
- Post operative antibiotics and pain medications are not recommended
- Routine follow up in GI clinic and follow up procedures at intervals noted above should be scheduled

Efficacy Metrics and Outcome Evaluation

The success of LNSCT is measured through multiple parameters:

Symptom Relief

Dysphagia improvement tracked using validated scores

Tumor Response

Reduction in tumor bulk and circumferential involvement documented via endoscopy

Long-Term Benefits

Enhancements in nutritional status, quality of life, and reduced need for subsequent interventions

Implementing Spray Cryotherapy in Clinical Practice

The integration of spray cryotherapy (SCT) into endoscopic practice necessitates a robust foundation of multidisciplinary collaboration. If such collaboration already exists, it can be leveraged to educate the care team on the role of SCT in managing esophageal cancer patients.

Multidisciplinary Collaboration

Close coordination with oncologists, surgeons, and radiation therapists ensures patient selection aligns with treatment goals. Multidisciplinary tumor boards provide an excellent platform for case discussions, enabling specialists to collectively determine the integration of SCT into a patient's broader care plan.

Infrastructure and Training

Programs require cryotherapy equipment, trained personnel, and experience with low complexity procedures to ensure team readiness. Training models have been developed to practice and hone skills prior to the first human experience. Remote and on site (hands on capable) proctorships are available and encouraged for new operators and programs.

Integration Across Settings

- **Hospital Outpatient Units:** Suitable for complex cases requiring advanced resources
- **Ambulatory Surgical Centers (ASCs):** Appropriate for straightforward, low-risk cases with adequate nursing and anesthesia support

Reimbursement Considerations

Spray Cryotherapy has standardized CPT codes with physician reimbursement and facility fees:

- CPT Code 43229- limited esophagoscopy with tissue ablation - RVU 3.49
    - Medicare national average reimbursement for facility fee- $3641
- CPT Code 43270- EGD with tissue ablation - RVU 4.0
    - Medicare national average reimbursement for facility fee- $2200
- SCT catheter list price $1995.00
- 3rd party / private payers are typically 1.5- 2x Medicare national average for facility fees

Research Gaps and Key Recommendations

Research Gaps and Future Directions

The session identified several areas requiring further exploration:

Comparative Trials: Evaluating SCT against other palliative therapies for dysphagia

Protocol Optimization: Refining the ideal number of cycles, cryogen types, and application techniques

Immunological Effects: Investigating potential immune activation and synergy with immunotherapy

Long-Term Studies: Examining the impact of SCT on survival, quality of life, and long-term outcomes

Key Recommendations

1. Multidisciplinary engagement by GI LNSCT champion. Position the case for LNSCT with the GI-MDT group
2. Infrastructure: capital equipment, staff training, MD training, ex vivo, in vivo simple case, in vivo complex case
3. HOPD vs ASC vs Both: Combination of business + clinical decisions (practice/division leadership in conjunction with GI LNSCT champion)
4. Patient Selection: Prioritize patients needing palliation who would be good candidates for LNSCT (as opposed to stenting or RT)
5. Procedure Timing: Align SCT with systemic and radiation therapies to maximize safety and efficacy
6. Safety Protocols: Adhere to strict suction and venting guidelines during procedures
7. Collaborative Approach: Maintain multidisciplinary oversight for optimal patient outcomes. Ideally, GI physicians are actively participating in the tumor board and develop interdisciplinary protocols
8. Treatment goals: Clinical goals: improve dysphagia (primary goal) & eliminate luminal disease (ideal secondary goal)