Diagnostic pathways and treatment options in oesophago-gastric cancer

1.45pm - 2.30pm

Mr Sacheen Kumar
Consultant Upper GI Surgeon
The Royal Marsden
Oesophago-Gastric Cancer

5th Most common cancer

Late Presentation

61.3% of patients have Palliative treatment

38 Specialist OG Cancer Centres in England

Time till definitive treatment – 65 days

Enormous Physical, Social and Psychological Impact
10 Year Net Survival Trends for Selected Cancers

- **Melanoma**: 90.3%
- **Breast**: 79.9%
- **Brain**: 13.9%
- **Oesophagus**: 12.7%
- **Lung**: 5.0%
- **Pancreas**: 1.1%

Year of Diagnosis
Oesophageal and gastric cancer - aetiology

**Oesophageal**
- Smoking
- Alcohol
- Reflux
- Barrett’s
- Obesity
- Achalasia
- Family History
- Corrosives

**Gastric**
- Smoking
- Alcohol
- Helicobacter Pylori
- Family history
- Previous stomach surgery
- Pernicious anaemia
Endoscopic Appearance of OG Cancer

Urgent Cross-Sectional Imaging, contacting Cancer Nurse Specialist and Referral to Upper GI Multidisciplinary Meeting
Staging for OG Cancer
CT scan Chest/Abdomen/Pelvis
$^{18}$F-FDG PET scan
Endoscopic Ultrasound (T1/T4 disease)
Peri-operative Pathway

Long and intensive - over 6 months

Pre-op
- Neo-adjuvant
- 3/4 cycles

Surgery
- Oesophagectomy
- Gastrectomy

Post-op
- Adjuvant
- 3/4 cycles
Staging laparoscopy and OGD

— Oesophago-gastric cancers require accurate staging prior to surgery

— Need to distinguish potentially curable from likely incurable disease

— 2019 EORTC Gastrointestinal Cancer Conference: Controversial issues in the multimodal primary treatment of gastric, junctional and oesophageal adenocarcinoma recommends staging laparoscopy to diagnose peritoneal involvement before starting neoadjuvant treatment in all gastric cancers and in oesophago-gastric junctional (OGJ) type II and III
Use of staging CT and CT PET

— With traditional use of Computed Tomography (CT) imaging alone, staging laparoscopy has been shown to change management in up to 40% of cases

— The staging ability of CT and its sensitivity in detecting small volume metastases is continually improving

— This is further enhanced with use of Positron Emission Tomography (PET)-CT
Advantages and limitations of CT PET

— FDG-PET has been shown to have a higher sensitivity for detection of metastatic disease compared to CT

— In oesophageal and OGJ FDG-PET led to upstaging 15% of patients from M0 to M1 disease and downstaging of 7% of the patients

— Overall sensitivity of FDG-PET/CT for detecting gastric cancer is lower than for most other malignancies

— Gastric cancer only PET avid in 65-80% (poor for diffuse type) and changes management in 5%.

— Limited efficacy for small lesions <5mm

— Potential for false-positive e.g., benign tumours, inflammatory processes
Methods

— Over the last 3 years, between 2016 – 2019

— Data was analysed from prospectively maintained electronic patient records at a tertiary referral cancer centre

— All patients with gastric, OGJ or oesophageal cancer undergoing a staging laparoscopy were included

— All patients were imaged pre-operatively with a staging CT scan and a PET-CT.
RMH Staging Laparoscopy Data

- 162 patients underwent staging laparoscopy (116 males, 72%)

- Median patient age was 65 (range 40-85) years

- Cancer types were 69 (42%) gastric and 93 (58%) oesophageal/OGJ; of these, 11 patients were classified as distal oesophageal, 24 were Siewert I, 32 were Siewert II and 26 were Siewert III

- Tumour types included adenocarcinoma in 161 patients, of those, 25 (15%) had signet ring morphology, and 1 Squamous Cell Carcinoma of the distal oesophagus

- Tumour stage was predominantly T3 (n=109, 67%) and T4 (n=32, 20%)
Results

— Staging laparoscopy **changed management in 31 (19%)** patients (25% in gastric and 15% in oesophageal/OGJ cancer).

— Previously undetected metastatic disease was seen in 15 patients (9%), with peritoneal disease (n=14) and liver lesions (n=1) observed.

— 12 patients (7%) had locally advanced disease

— 4 (2%) patients were judged unfit for major surgery
Study Conclusions

- Staging laparoscopy continues to be an important diagnostic modality in the treatment pathway of oesophageo-gastric cancers

- It reduces the risk of surgery without benefit for the patient, especially in gastric and OGJ Type 2 & 3 cancers

- Despite recent advances in imaging techniques and expert interpretation, there are still limitations of radiology alone in assessing extent of disease and suitability for curative resection.
Key Trials in Oesophago-Gastric Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer


Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial


on behalf of the FLOT-4-ALO Investigators
Surgery for OG Cancer
Aim of Resection

- **Pre-op**
  - Neo-adjuvant
  - 3/4 cycles

- **Surgery**
  - Oesophagectomy
  - Gastrectomy

- **Post-op**
  - Adjuvant 3/4 cycles

Complete resection of primary tumour (Ro)

Clear margins

**Lymphadenectomy (>15 nodes)**
Siewert AEG-Classification

Centre of tumour 2cm above or below gastro-oesophageal junction

Defining the centre is NOT easy

- Endoscopy
- Imaging

Decisions based only on the centre? Too simplistic

Mobilisation - blood supply of the stomach
Lymph nodes draining the stomach

**Lesser curvature group**
1. Paracardiac nodes
2. Lesser curvature nodes
3. Left gastric artery nodes
4. Common hepatic artery nodes
5. Celiac axis nodes
6. Hepatoduodenal ligament nodes

**Greater curvature group**
7. Greater curvature nodes
8. Pyloric nodes
9. Gastroduodenal nodes
10. Gastroepiploic nodes
11. Pancreaticoduodenal nodes

**Pancreatic and splenic group**
12. Splenic nodes
13. Pancreaticosplenic nodes

**Regional group**
14. Retropancreatic nodes
15. Para-aortic nodes
16. Mesenteric nodes
Pattern of lymph node spread
En bloc resection

EORTC Consensus - St Gallen 2012

Type I – Oesophago-Gastrectomy

Type II – Oesophago-Gastrectomy or Extended Total Gastrectomy

Type I & II – Mediastinal Lymphadenectomy
  – 2 field

Type III – Extended Total Gastrectomy
Minimally Invasive Approach

Original Article

Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer


Background
Postoperative complications, especially pulmonary complications, affect more than half the patients who undergo open esophagectomy for esophageal cancer. Whether hybrid minimally invasive esophagectomy results in lower morbidity than open esophagectomy is unclear.

Methods
We performed a multicenter, open-label, randomized, controlled trial involving patients 18 to 75 years of age with resectable cancer of the middle or lower third of the esophagus. Patients were randomly assigned to undergo transthoracic open esophagectomy (open procedure) or hybrid minimally invasive esophagectomy (hybrid procedure). Surgical quality assurance was implemented by the credentialing of surgeons, standardization of technique, and monitoring of performance. Hybrid surgery comprised a two-field abdominal–thoracic operation (also called an Ivor–Lewis procedure) with laparoscopic gastric mobilization and open right thoracotomy. The primary end point was intraoperative or postoperative complication of grade II or higher according to the Clavien–Dindo classification (indicating major complication leading to intervention) within 30 days. Analyses were done according to the intention-to-treat principle.

Results
From October 2009 through April 2012, we randomly assigned 103 patients to the hybrid-procedure group and 104 to the open-procedure group. A total of 312 serious adverse events were recorded in 110 patients. A total of 37 patients (36%) in the hybrid-procedure group had a major intraoperative or postoperative complication, as compared with 67 (64%) in the open-procedure group (odds ratio, 0.31; 95% confidence interval [CI], 0.18 to 0.55; P<0.001). A total of 18 of 102 patients (18%) in the hybrid-procedure group had a major pulmonary complication, as compared with 31 of 103 (30%) in the open-procedure group. At 3 years, overall survival was 67% (95% CI, 57 to 75) in the hybrid-procedure group, as compared with 55% (95% CI, 45 to 64) in the open-procedure group; disease-free survival was 57% (95% CI, 47 to 66) and 48% (95% CI, 38 to 57), respectively.

Conclusions
We found that hybrid minimally invasive esophagectomy resulted in a lower incidence of intraoperative and postoperative major complications, specifically pulmonary complications, than open esophagectomy, without compromising overall and disease-free survival over a period of 3 years. (Funded by the French National Cancer Institute; ClinicalTrials.gov number, NCT00937456.)
Oesophago-Gastric Junctional Adenocarcinoma
Extent of resection
Roux-en-Y gastrojejunostomy
Roux-en-Y oesophagojejunostomy
Survival
One year age-standardised net survival for adults 2011-2015 by Cancer Alliance and STP - Oesophageal Cancer

<table>
<thead>
<tr>
<th>STP</th>
<th>Patients</th>
<th>Value (%)</th>
<th>Lower CI</th>
<th>Upper CI</th>
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<tr>
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Source: Office of National Statistics sourced from National Cancer Registration Service
https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/geographicpatternsofcancersurvivaline ngland

RAG rating (95% confidence interval)
Green highlight - Rate is better than England overall rate
Red highlight - Rate is worse than England overall rate
# One year age-standardised net survival for adults 2011-2015 by Cancer Alliance and STP - Stomach Cancer

<table>
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<th>STP</th>
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<td>Bristol, North Somerset and South Gloucestershire (*)</td>
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<td>Birmingham and Solihull (*)</td>
<td>614</td>
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<td>Bath, Swindon and Wiltshire (**)</td>
<td>379</td>
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<tr>
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<td>England</td>
<td>27,496</td>
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</tbody>
</table>


**RAG rating (95% confidence interval)**
- **Green highlight** - Rate is better than England overall rate
- **Red highlight** - Rate is worse than England overall rate
Innovations in OG Cancer
Improving Outcomes in OG cancer

— Incidence of OG Cancer – endoscopy-based screening programmes
— are not cost-effective

— Historically poor awareness of the disease

— Ongoing Studies – International UGI Surgery Collaboration

— The Future
  • Early detection of the disease
  • Personalised Medicine & new chemotherapeutic treatments
  • Novel Endoscopic, Interventional & Surgical Approaches
  • Optimal Staging techniques
Early Diagnosis Technologies

A trial looking at the Cytosponge test in GP surgeries for people with heartburn symptoms (BEST3)
Early Diagnosis Technologies

Colorectal cancer screening with odour material by canine scent detection
Hideto Sonoda, Shunji Kohnoe, Tetsuro Yamazato, Yuji Satoh, Gouki Morizono, Kentaro Shikata, Makoto Morita, Akihiro Watanabe, Masaru Morita, Yoshihiro Kakeji, Fumio Inoue, Yoshihiko Maehara
Gut 2011; 60: 814-819

— Volatile Organic Compounds (VOCs) routinely measured in:
  • Assessment of environmental contamination
  • Flavour and fragrance industry
  • Counter-Terrorism

— Endogenous VOCs potentially hold the key to identification of biomarkers for underlying disease processes
Early Diagnosis Technologies

Mass Spectrometric Analysis of Exhaled Breath for the Identification of Volatile Organic Compound Biomarkers in Esophageal and Gastric Adenocarcinoma

Sachen Kumar, MRCS,* Jucheng Huang, PhD,* Nina Abbassi-Ghadi, MRCS,* Hugh A. Mackenzie, MRCS,* Kirill A. Veselkov, PhD,* Jonathan M. Hoare, PhD, FRCP,† Laurence B. Lovat, PhD, FRCP,‡ Patrik Španěl, PhD,§ David Smith, PhD, FRS,¶ and George B. Hanna, PhD, FRCS*

Mass-Spectrometry Analysis of Mixed-Breath, Isolated-Bronchial-Breath, and Gastric-Endoluminal-Air Volatile Fatty Acids in Esophagogastric Cancer

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Received: January 9, 2019
Accepted: January 30, 2019
Published: January 30, 2019
Endoscopy & AR
Robotic Surgery
Robotic Surgery
Communication

In Vivo Endoscopic Tissue Identification by Rapid Evaporative Ionization Mass Spectrometry (REIMS)

Dr. Julia Balog, Dr. Sacheen Kumar, James Alexander, Ottmar Golf, Dr. Juzheng Huang, Tom Wiggins, Nima Abbasi-Ghadi, Dr. Attila Eyedi, Dr. Sandor Kacska, James Knross. ... See all authors

First published: 6 August 2015 | https://doi.org/10.1002/anie.201502770 | Cited by:29
Multivariable analysis comparing lipidomic profiles (m/z 600-1000) of esophageal adenocarcinoma (EA, red), Barrett’s dysplasia (BD, orange), Barrett’s metaplasia (BM, blue), inflamed esophageal epithelium (IEE, light green) and healthy esophageal epithelium (HEE, dark green). a) Principal component analysis score plot. Each point is the average of multiple mass spectra representative of that tissue type within a single sample from one patient. b) representative mass spectra of tissue types and; c) Heat map of 86 samples; d) Recursive Maximum Margin criterion (RMMC) supervised analysis score plot of cohort 2; e) Leave one out cross-validated RMMC score plot as per confusion matrix; f) Confusion matrix of leave one out internal cross validation with Mahalanobis distance classifier.
Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors

- Reflux
- Microbiome
- Metabolism
- Lipid peroxidation
- Reactive aldehydes
- Effect of pH
- Schiff base adduction
- DNA mutation
- Protein denaturation
- Lipid carbonylation

A non-endoscopic device to sample the oesophageal microbiota: a case-control study

Daffodil R Fels Elliott, Alan W Walker, Maria O Donovan, Julian Parkhill, Rebecca C Fitzgerald

Decreased microbial diversity in oesophageal adenocarcinoma tissue compared with tissue from healthy control patients

Selected Ion Flow Tube-MS Analysis of Headspace Vapor from Gastric Content for the Diagnosis of Gastro-Esophageal Cancer

- Sacheen Kumar, Juheng Huang, Julia R. Cushnir, Patrik Španěl, David Smith, and George B. Hanna

- No difference in proton pump inhibitor/H2-receptor antagonist use amongst 3 groups
Thank you