February | 13th-14th, 2020
Bologna (Italy), Royal Hotel Carlton

Translational research for the management of **Barrett's esophagus** and **esophageal adenocarcinoma**: *updates and proposals*

Final Program

On the cover:

Archiginnasio Palace, XVI Century (1562-1563)

Once main building of the University of Bologna, now house of the Municipal Library and Anatomical Theatre

Dear Colleagues,

We are happy to welcome you in **Bologna** at the **first EACSGE Symposium (Esophageal Adenocarcinoma Study Group Europe)** on **February 13-14th 2020.**
The EACSGE is a joined effort of the Universities of Bologna, Genova, Helsinki, of the Amsterdam University Medical Centers, and the National Oncologic IRST/IRCCS (Scientific Institute for Treatment and Research) of Meldola, Italy; the EACSGE has been recently established to address the rising problem of a highly malignant disease which we believe can only be dealt with through implementation of novel state-of-the-art translational and fundamental research. Esophageal adenocarcinoma indeed requires innovative approaches, to prevent its further increase and to improve patient outcomes. The EACSGE believes that this can be achieved only through bringing together all experts in the field of esophageal adenocarcinoma and to initiate effective collaborations. These collaborative efforts will aim at bringing experts from different disciplines together to develop and implement efficient screening and surveillance programs, and to apply urgently required innovative combinatorial treatment strategies.
The recent insights in the biological make up of esophageal adenocarcinoma and its precursor lesion, Barrett's esophagus, offers unique possibilities to achieve such goals. Therefore, the field of translational research on esophageal diseases is expanding and holds great promise for improving therapy and patient management. This first EACSGE Symposium will have a clear focus on the outcomes of disease biology and evolution; in addition, innovative study protocols, translational and early clinical studies on esophageal adenocarcinoma and Barrett's esophagus will be presented. The discussion among eminent biologists, oncologists, pathologists, gastroenterologists and surgeons, will produce research programs aimed to identify new therapeutic strategies based on the identification of case by case biological patterns by means of bio-molecular prognostic and progression markers.
This multi-disciplinary meeting is offered to clinician and scientists in the field of genomic medicine, pathology, gastroenterology, oncology and surgery with special interest in esophageal diseases.

Looking forward to meet you in Bologna,

Sandro Mattioli

Sheila K. Krishnadath

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European Society for Diseases of the Esophagus

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Italian Society for the Study of Esophageal Diseases

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Jarmo **Salo,** *Helsinki (Finland)*

Marco **Seri,** *Bologna (Italy)*

Nick **Stoecklein,** *Dusseldorf (Germany)*

Richard **Turkington,** *Belfast (Ireland)*

Richard **Van Hillgersberg,** *Utrecht (The Netherlands)*

Jan **Van Lanschot,** *Helvoirt (The Netherlands)*

Kenneth **Wang,** *Rochester (USA)*

Thursday | February 13th

08.30-09.15 Registration and Welcome Coffee

09.15-09.30 Welcome and introduction
Sandro Mattioli, Marco Seri, Bruno Biagi

09.30-10.00 **Opening Lecture**
Introduced by Sheila K. Krishnadath
Lessons from the Esophageal Adenocarcinoma Genome
Rebecca Fitzgerald

SESSION 1
Barrett's esophagus: what does stand and what is upcoming
Chairs: Franco Bazzoli, Michael Quante

10.00-10.30 Barrett's esophagus: is it time to screen for Barrett's esophagus?
Kenneth Wang

10.30-11.00 Pitfalls in the histological grading of Barrett's esophagus
Sybren L. Meijer

11.00-11.15 Discussion

SESSION 2
Therapeutic options and prognostic indicators for EAC: what does stand
Chairs: Antoon Lerut, Matthew Read

11.15-11.30 Current standards and results of surgical therapy
Riccardo Rosati

11.30-11.45 Neo-adjuvant and adjuvant therapy for EAC
Salah-Eddin Al -Batran

11.45-12.00 Strength and weakness of the TNM staging systems
Wayne Hofstetter

12.00-12.15 A histopathological classification of EAC
Roberto Fiocca

12.15-12.30 Discussion

12.30-14.00 Lunch Break

12.45-13.15 **LUNCH SYMPOSIUM***
** not accredited CME/EACCME*
Flyer included

SESSION 3
EAC Prognostic indicators: what is upcoming
Chairs: Andrea Ardizzoni, Roberto Fiocca

14.00-14.15 Role of CTCs
Nick Stoecklein

14.15-14.30 Role of SMAD4 expression
Luca Mastracci

14.30-14.45 Expression profiles of EC/EAC
Adam Bass

14.45-15.00 Ct-DNA as a tool in the clinical management of EAC
Wayne Phillips

15.00-15.15 Role of Micro RNAs
Elena Bonora

15.15-15.30 Discussion

15.30-16.00 **Lecture**
Chair: Giovanni Martinelli
Innate immunity, inflammation and cancer
Paola Allavena

16.00-16.30 Coffee Break

SESSION 4

Immune Therapies and the role of the microbiome

Chairs: Adam Bass, Stefano Cascinu, Wayne Phillips

16.30-16.50 Car-T cell therapy for solid cancer
Giovanni Martinelli

16.50-17.10 Microbiome overview
Giovanni Barbara

17.10-17.30 Gut microbiote and esophageal cancer
Gianluca Ianiro

17.30-17.50 Oncolytic virus therapy
Toni Ibrahim

17.50-18.15 Discussion

18.15-18.30 Closing of the day

Short Address
Introduced by Sandro Mattioli and Marco Seri
The institutional supports to research in Europe
Antonino Rotolo, Vice Rector for Research - Alma Mater Studiorum - University of Bologna

18.45-19.30 **EACSGE WORK MEETING SESSION 1** - Imperiale Hall*
** not accredited CME/EACCME*

BARRETT's and EAC. Discussion on EACSGE cooperative and single centres data, on new research proposals

Faculty and congress attendees are welcome

20.30 Welcome Dinner

Friday | February 14th

8.00-8.45 **EACSGE WORK MEETING SESSION 2** - Imperiale Hall*
** not accredited CME/EACCME*

BARRETT's and EAC. Discussion on EACSGE cooperative and single centres data, on new research proposals

Faculty and congress attendees are welcome

SESSION 5
8.45-10.00
Oral Presentations
Chairs: Antonietta D'Errico, Jari Rasanen

1. EXPRESSION OF COX2 AND P53 IN RAT ESOPHAGEAL CANCER INDUCED BY REFLUX OF DUODENAL CONTENTS
N.H Hashimoto Naoki
Sanda City Hospital, Department of Emergency Medicine, Sanda, Japan

2. GENOMIC BIOMARKERS FOR CANCER RISK IN BARRETT'S ESOPHAGUS: AN UPDATE ON THE LONGITUDINAL DUTCH BARRETT'S ESOPHAGUS COHORT
S.J.M. Hoefnagel[1], W.M. Westra[1], M.R. Timmer[1], P. Martinez[2], E. Klaver[3], C.T. Lau[1], S. Calpe[1], M. del C. Sancho-Serra[1], D. Straub[1], A.M. Baker[2], A.M. Rygiel[1], W.D. Rosmolen[3], S. L. Meijer[5], F.J.W. ten Kate[5], M.G.W. Dijkgraaf[7], R.C. Mallant-Hent[7], A.H.J. Naber[7], A.H.A.M. van Oijen[7], L.C. Baak[7], P. Scholten[7], C.J.M. Böhmer[7], C.C. Maley[6], T.A. Graham[2], J.J.G.H.M. Bergman[3], [7], K.K. Krishnadath[1, 3, 7]
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[5]Department of Pathology, Amsterdam University Medical Centers,University of Amsterdam, Amsterdam, the Netherlands;
[6]Biodesign Institute, School of Life Sciences, Arizona State University, Tempe, Arizona, the United States of America
[7]Gastroenterological Association, Amsterdam, The Netherlands

3. SINGLE CELL RNA SEQUENCING OF INDIVIDUAL EAC ORGANOIDS REVEALS HETEROGENEITY OF STEM CELL LIKE POPULATIONS

Derouet. M, Gavin W. Wilson, Gail E. Darling and Jonathan C. Yeung.
University Health Network, Division of Thoracic Surgery, Toronto, Canada

4. THE NORTHERN IRELAND BARRETT'S REGISTER: MOLECULAR BIOMARKERS TO PREDICT PROGRESSION OF BARRETT'S OESOPHAGUS (BO) TO OESOPHAGEAL ADENOCARCINOMA (OAC)

Richard C Turkington, Jaine K Blayney, Kathleen Curtius, Marnix Jansen, Damian McManus, Brian T Johnston, Helen G Coleman
Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, United Kingdom

5. INDOCYANINE GREEN SPEED BEFORE GASTRIC TUBULIZATION AS A MAIN OBJECTIVE PARAMETER TO EVALUATE GASTRIC MICROCIRCULATION DURING IVOR-LEWIS ESOPHAGECTOMY

Parise P.[1], Talavera-Urquijo E., Olivari G.[1], Cossu A.1, Barbieri L.[1], Carresi A.[1], Di Furia M.[1], Rosati R.
[1.] San Raffaele University Hospital - Milano (Italy) / Gastrointestinal Surgery Unit

6. THE GENERATION AND VALIDATION OF FOUR NEW ESOPHAGEAL CANCER CELL LINES

Matthew Read[1], [2] ,Wayne Phillips[1, 2], David Liu[1,] Glen Guerra[1], Cuong Duong[1], Ingrid Franken[3], Richard van Hillegersberg[3], Kausilia Krishnadath[4] & Nicholas Clemons[1]
[1]Division of Cancer Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.
[2]Department of Surgery (St Vincent's Hospital), The University of Melbourne, Parkville, Victoria, Australia.
[3]Department of Surgery, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
[4]Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands.

7. A CHEMORADIOTHERAPY TREATMENT RESPONSE MRNA SIGNATURE AS PREDICTOR FOR ESOPHAGEAL ADENOCARCINOMA TREATED ACCORDING TO THE CROSS REGIMEN

S.J.M. Hoefnagel[1, 2], J. Koster[3], W.J. Koemans[4], J.M. van Dieren[5], J.W. van Sandick[4], L.L. Kodach[6], S. Calpe[1], S. L. Meijer[7, 8], C. M del Sancho-Serra[1], H.N. Khan[1], H.W.M. Van Laarhoven[8], M.I. Van Berge Henegouwen[8], S.S. Gisbertz[8], M.C.C.M. Hulshof[8], K.K. Krishnadath[1, 2, 8*]

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[7]Department of Pathology, Amsterdam University Medical Centers, Amsterdam, the Netherlands;
[8]Esophageal Cancer Workgroup, University Medical Centers, Amsterdam, the Netherlands; Cancer Center Amsterdam.

8. MULTIMODAL THERAPY IN ESOPHAGEAL CANCER BEYOND CLINICAL TRIAL: SINGLE CENTRE EXPERIENCE

Alberti L[1], Giacopuzzi S[1], Weindelmayer J[1], De Pasqual C.A.[1], Torroni L.[2], Verlato G.2, De Manzoni G[1]

[1]Department of General Surgery and Upper G.I. Division, University Hospital of Verona, Italy
[2] Department of Diagnostics and Public Health, University of Verona, Italy

9. DIAPHRAGMATIC HERNIA AFTER IVOR-LEWIS OESOPHAGECTOMY: ANALYSIS OF RISK FACTORS AND SURGICAL REPAIR RESULTS

Parise P.[1], Puccetti F.[1], De Pascale S.[2], Cossu A.[1], Talavera-Urquijo E.[1], Carresi A.[1], Olivari G.[1], Fumagalli R. U.[2], Rosati R.[1]

[1] Gastrointestinal Surgery Unit - San Raffaele Hospital - Milan - Italy
[2] Digestive System Surgery Unit - European Institute of Oncology - Milan - Italy

SESSION 6
Novel findings in Barrett's esophagus
Chairs: Adam Bass, Kenneth Wang

10.00-10.15 Screening methods for Barrett's esophagus
Kenneth Wang

10.15-10.30 Novel targeted treatment for Barrett's esophagus
Sheila K. Krishnadath

10.30-10.45 Immune models for Barrett's esophagus
Michael Quante

10.45-11.00 Prognostic profiles of Barrett's esophagus
Sanne Hoefnagel

11.00-11.15 Discussion

11.15-11.45 Coffee Break

11.45-12.10 **Lecture**
Chair: Giovanni Martinelli
Technologies in cancer research and diagnosis
Stefano Pileri

SESSION 7
Molecular targets and response predictors in EAC
Chairs: Sheila K. Krishnadath, Marco Seri

12.10- 12.25 EAC expression profiles and response predictors
Sanne Hoefnagel

12.25- 12.40 P53 as a response predictor after primary surgery
Elena Bonora

12.40-12.55 Restoring p53 function for treatment of cancer
Giovanni Martinelli

12.55-13.10 Targeting the p53-MDM2 pathway
Cristina Papayannidis

13.10-13.20 Discussion

13.20-14.15 Lunch Break

PARALLEL SESSIONS 8

SESSION A / Workgroup Session of the BERN Group - Saturno Hall

Chairs: Adam Bass, Sheila K. Krishnadath

14.15-14.30 Epidemiological data on Barrett's esophagus in Northern Ireland
Richard Turkington

14.30-14.45 Population screening options
Michael Quante

14.45-15.00 Barrett's esophagus treatment options
Sheila K. Krishnadath, Michael Quante

15.00-15.15 Proposals and discussion

SESSION B / Redefining Surgical Therapy - Imperiale Hall

Chairs: Giovanni De Manzoni, Jarmo Salo

14.10-14.20 Preliminary results from the PRESANO and SANO studies
Jan Van Lanschot

14.20-14.30 Siewert type II EAC: Ivor Lewis or total gastrectomy?
Sandro Mattioli

14.30-14.50 Clinical versus Pathology staging today
Jari Räsänen

14.50-15.00 Does MRI improve Clinical Staging ?
Richard Van Hillgersberg

15.00-15.15 Proposals and discussion

SESSION 9

Diagnosis and prognosis, therapy and follow up for EAC: what next?

Chairs: Salah-Eddin Al-Batran, Giovanni Martinelli, Sandro Mattioli

15.15-15.30	Which prognostic indicators for the therapeutic strategy? *Wayne Hofstetter*
15.30-15.45	Endoscopic biopsies and tumor heterogeneity *Antonietta D'Errico*
15.45-16.00	The role of medical oncology *Salah-Eddin Al –Batran*
16.00-16.15	New pathology related survivals and current therapeutic guidelines: the EACSGE point of view *Stefano De Pascale*
16.15-16.30	Discussion step 1
16.30-16.45	The EACSGE proposals for future study protocols *Giovanni Martinelli, Sandro Mattioli*
16.45-17.00	Discussion step 2 *Discussants: Giovanni De Manzoni, Uberto Fumagalli Romario, Lorenzo Gervaso, Waine Hofstetter, Magnus Nilsson, Riccardo Rosati, Jan Van Lanschot*
17.00-17.15	Prize for the best oral presentation and closing remarks

NOTES

GENERAL INFORMATION

MEETING VENUE

Royal Hotel Carlton
Via Montebello, 8 - Bologna (Italy)
Ph. +39 051 249361
www.monrifhotels.it

How to reach the Venue

The Royal Hotel Carlton is located in the centre of Bologna, walking distance from the Railway Station and Piazza Maggiore.
By car: From the highway, exit n. 7/City Centre - Fair,following the indications for the Railway Station - Set the navigation system for Via Milazzo 6 to avoid the restricted traffic zone. Private Parking of the Hotel available.
By plane: Guglielmo Marconi International Airport is 20 minutes from the Hotel.
Airbus shuttle services (AEROBUS) departs every 20 minutes from the Airport to the Station.

REGISTRATION FEE

Online registration is available on the webiste **www.eacsge.org** and on **www.iec-srl.it** or scanning **QR code** here below

Available places: 150

Physicians

Before December 18th 2019	€ 450,00
From December 19th 2019	€ 530,00

Trainees/Residents

Before December 18th 2019	€ 200,00
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(Costs including VAT 22%)

The registration fee covers:

- Admission to scientific sessions
- Congress kit
- Certificate of attendance
- Coffee breaks and lunches
- Welcome dinner (February 13th, Royal Hotel Carlton)

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English is the official language of the Meeting. Simultaneous translation is not provided.

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Facilities will be available for computer presentations.
The Slide Center with PC will be available in the main hall for check and preview the presentations. Speakers are kindly requested to deliver their presentation to the slide center at least one hour before the session starts.

CERTIFICATE OF ATTENDANCE

The certificate of attendance will be available, on request, at the end of the Congress at the Secretariat Desk.

PRIZE FOR THE BEST ORAL PRESENTATION

The Scientific Committee with the chairs of the session 5, will elect a prize on the basis of the scientific content of the presentation, the quality of exposition and discussion.

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ABSTRACT

1. EXPRESSION OF COX2 AND P53 IN RAT ESOPHAGEAL CANCER INDUCED BY REFLUX OF DUODENAL CONTENTS

N.H Hashimoto Naoki
Sanda City Hospital, Department of Emergency Medicine , Sanda, Japan

(Aim) Reflux of duodenal contents contributes to the development of esophageal mucosal lesion. Esophageal cancer after total gastrectomy has been associated with the reflux of duodenal content (biliary and pancreatic juice) into the esophagus.
This study is to determine which fraction of the duodenum content reflux, pancreatic juice or bile acids contributes to the development of esophageal cancer.
(Methods 8 week Wistar Rat were used.
1.Reflux of Pancreatic juice and Bile(TG): End-to-end esophago-duodenostomy with total gastrectomy (n=27) was performed to produce pancreatic juice and bile reflux. 2.Reflux of Pancreatic Juice (TG+B):End-to-end esophago-duodenostom with total gastrectomy. Then, a bypass operation of the upper bile duct was made 25cm below the esophagoduodenostomy anastomosis to produce only pancreatic reflux. Choledocho-jejunostomy was performed.(n=12) 3.Sham group (n=5)
Forty weeks after operation, all rats were euthanized and the esophagus was evaluated histologically. Esophageal injury was evaluated by macroscopic and microscopic findings.
(Results)1.Macroscopic finding: In TG rats, the esophageal wall was thickened and sever inflammation. There was a small polypoid tumor in the lower esophagus in TG. The tumor is SCC and ADC. But TG+B was not sever inflammation, moreover the esophagus of TG+B did not reveal any pathological findings. 2. Microscopic findings: TG showed histological features of esophagitis including marked hyperplastic changes with increased thickness of squamous epithelium, hyperkeratosis and regenerative changes with papillomatosis and basal cell hyperplasia. By the way, TG+B showed slightly dysplasia of the esophagus.
In TG, we detect erosion (100%), regenerative hyperplasia (100%), CLE(40%), sever dysplasia (100%), SCC(40%) and ADC(30%).
In TG+B, we detect erosion(0%), regenerative hyperplasia(100%),CLE(0%), mild dysplasia (40%), SCC(0%) and ADC(0%).
(Conclusion) The reflux of pancreatic juice alone is probably not significant development of esophageal cancer after total gastrectomy compared to the reflux of bile and pancreatic juice. Pancreatic juice reflux appears to exert a co-carcinogenic effect when combined with bile.

2. GENOMIC BIOMARKERS FOR CANCER RISK IN BARRETT'S ESOPHAGUS: AN UPDATE ON THE LONGITUDINAL DUTCH BARRETT'S ESOPHAGUS COHORT

S.J.M. Hoefnagel[1], W.M. Westra[1], M.R. Timmer[1], P. Martinez[2], E. Klaver[3], C.T. Lau[1], S. Calpe[1], M. del C. Sancho-Serra[1], D. Straub[1], A.M. Baker[2], A.M. Rygiel[1], W.D. Rosmolen[3], S. L. Meijer[5], F.J.W. ten Kate[5], M.G.W. Dijkgraaf[7], R.C. Mallant-Hent[7], A.H.J. Naber[7], A.H.A.M. van Oijen[7], L.C. Baak[7], P. Scholten7, C.J.M. Böhmer[7], C.C. Maley[6], T.A. Graham[2], J.J.G.H.M. Bergman[3, 7], K.K. Krishnadath[1, 3, 7]

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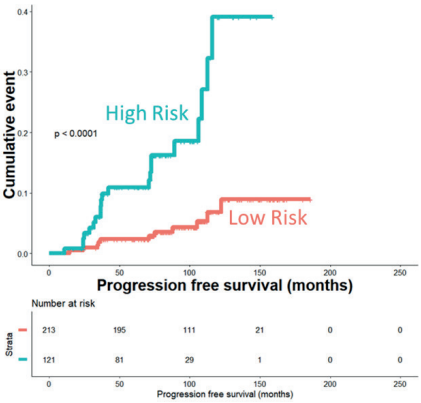
[3]Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Amsterdam, the Netherlands;
[4]Department of Oncogenomics, Amsterdam University Medical Centers, Amsterdam, the Netherlands;
[5]Department of Pathology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands;
[6]Biodesign Institute, School of Life Sciences, Arizona State University, Tempe, Arizona, the United States of America
[7]Gastroenterological Association, Amsterdam, The Netherlands

Barrett's esophagus (BE) is the precursor of esophageal adenocarcinoma (EAC). Malignant degeneration of non-dysplastic BE (NDBE) patients occurs infrequently. Robust biomarkers that predict long term cancer risk are required to improve surveillance. In previous studies, we identified a set of genomic abnormalities as potential biomarkers (1, 2), to improve surveillance strategies. Here, we test their robustness over longer periods of time.

In this study, numerical aberrations for CEP7, CEP17 and structural abnormalities for c-MYC, p16, p53, Her-2/neu and 20q earlier assessed by DNA FISH, were used to determine (clonal diversity) marker scores. These markers were combined with clinical variables using Cox regression modeling, bootstrapping and leave-one-out analyses were applied.

A total of 334 NDBE patients from 6 community hospitals (n=220) and one academic center (n=114) were included. Median age was 60 years (IQR= 16) and average circumferential Barrett's length (CBL) was 2 cm (SD 4cm). The median follow-up time was 87 months (IQR 40). The annual progression rate to HGD or EAC was 1.3%. A multivariate prediction model including the (borderline) significant variables age and CBL, and clonal diversity score over marker set CEP7, CEP17, 20q and c-MYC, resulted in an AUC 0.62, with a sensitivity of 0.66 and a specificity of 0.67 (risk score cutoff at 1.357). This model defines a high risk population with an annual progression rate of 2.9%, versus 0.63% in the low risk group (figure).

We propose that implementation of the model can identify NDBE patients that require more frequent surveillance or endoscopic treatment.



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3. SINGLE CELL RNA SEQUENCING OF INDIVIDUAL EAC ORGANOIDS REVEALS HETEROGENEITY OF STEM CELL LIKE POPULATIONS

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OBJECTIVE: To investigate the transcriptional programs of EAC tumour cells using patient derived organoids.

METHODS: EAC organoids were established from endoscopic biopsies from 4 different patients. Based on their morphology, individual organoids were isolated and dissociated into single cell suspensions. The 10X Genomics platform was used for single cell RNA sequencing.

RESULTS: Individual intestinal or cystic type organoids were isolated. The number of single cells recovered after 10X sequencing was 1646, 1926, 923 and 784 for the two intestinal and two cystic organoids respectively. For the two intestinal populations the samples could be divided into stem-like (905/1646 and 1472/1926) and differentiated populations. Interestingly, we observed differences in the number of cycling cells in these Lgr5+ stem-like populations (905/905 and 337/1926). For the cystic samples the two populations could also be divided into stem-like populations (758 / 923 and 284/784) and differentiated populations. We also observed cell cycle differences in the Lgr5+ stem-like populations in these samples (387 / 758 and 122 / 284). RNA velocity analyses on each sample verified a differentiation trajectory from the stem-like to the differentiated cells.

CONCLUSIONS: Studying EAC organoids provides us with the ability to profile the transcriptional programs of progenitor-like cells, which are difficult to isolate from gross tumor. We demonstrate that we can isolate individual organoids and study them at single-cell resolution to evaluate the different types of organoid progenitor cells based on their morphology.

4. THE NORTHERN IRELAND BARRETT'S REGISTER: MOLECULAR BIOMARKERS TO PREDICT PROGRESSION OF BARRETT'S OESOPHAGUS (BO) TO OESOPHAGEAL ADENOCARCINOMA (OAC)

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OBJECTIVE: The incidence of oesophageal adenocarcinoma (OAC), has risen by 50% in the UK in the last 25-30 years and five-year survival is 15%; highlighting the need for better preventative/early diagnosis strategies. Current Barrett's oesophagus (BO) surveillance strategies are over-diagnosing low risk non-progressive disease, while under-diagnosing high-risk life-threatening lesions. New approaches are required to identify non-dysplastic BO (NDBO) lesions at high risk of progression to High Grade Dysplasia (HGD)/OAC to facilitate endoscopic therapy or increased surveillance.
Using the Northern Ireland Barrett's Register, one of the largest BO population-based data and tissue resources available worldwide, our project will develop a molecular signature that may be applied in clinical practice to stratify BO patients according to cancer risk, leading to changes in patient management to maximise benefit and reduce harms.
METHODS: We analysed 16 FFPE endoscopic biopsy samples (7 NDBO, 9 HGD) using the Illumina TruSeq RNA exome panel in order to assess data quality for future biomarker discovery. HGD cases were matched to a NDBO control and biopsies were obtained through the NI Biobank. After pathological assessment for the presence of BO, combined DNA/RNA extraction was performed followed by profiling using the Illumina TruSeq RNA exome panel. Clustering-based analysis of the RNAseq data was carried out to identify transcriptional changes associated with NDBO/HGD.
We will now perform a nested case-control study of 200 case-control pairs of BO patients diagnosed between 1993 and 2016 with biopsy proven intestinal metaplasia. Cases will be BO patients who developed HGD/OAC more than 12 months after initial BO diagnosis and will be matched (on age, sex, year of BO diagnosis) to a BO control who has not developed HGD/OAC. Following identification of relevant molecular subgroups we will embark on signature generation to identify a gene signature capable of predicting progression to HGD/OAC in cases of NDBO.
RESULTS: Principle components analysis and hierarchical clustering showed clear separation between NDBO and HGD samples confirming the reliability and utility of the RNAseq data. Three subgroups were evident, two with distinct phenotypes (NDBO or HGD) and one mixed group. A similarity mapping (propensity score) analysis between a public dataset (GSE100843) of normal mucosa and BO samples (both with varying degrees of dysplasia) was carried out with respect to a dataset of normal and OAC samples (GSE92396). The results demonstrated transcriptional similarities between OAC, HGD and NDBO indicating that gene expression changes in tumours are represented in the earliest pre-malignant lesions.
We applied the Almac Diagnostics claraT assay which provides expression data of 62 unique gene expression signatures classified by the Hallmarks of Cancer. HGD samples demonstrated higher expression of immune-oncology and genomic instability signatures in keeping with previous studies showing the prevalence of aneuploidy, deficiencies in DNA repair and increasing mutational burden in dysplastic samples. We now seek to apply this powerful RNA sequencing methodology to the identification of biomarkers in a cohort of matched progressor and non-progressor NDBO samples.
CONCLUSIONS: Our results demonstrate the feasibility of RNAseq for biomarker discovery in BO. We will now develop a signature to identify BO patients at highest cancer risk, thereby enabling targeting of surveillance/interventions to maximise benefit for, and reduce harm to, BO patients.

5. INDOCYANINE GREEN SPEED BEFORE GASTRIC TUBULIZATION AS A MAIN OBJECTIVE PARAMETER TO EVALUATE GASTRIC MICROCIRCULATION DURING IVOR-LEWIS ESOPHAGECTOMY

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1. San Raffaele University Hospital - Milano (Italy) / Gastrointestinal Surgery Unit

OBJECTIVE: Ivor-Lewis esophagectomy (IL-E) is the procedure of choice for surgical treatment of distal esophagus and cardia cancer. Anastomotic leakage (AL), mainly due to gastric conduit (GC) ischemia, is the most fearsome complication. Intraoperative indocyanine green fluorescence angiography (ICG-FA) is a new technique for blood supply evaluation but which objective parameters should be measured is still unclear. Aim of this study was to identify which objective or subjective parameters at ICG-FA are associated to AL.

METHOD: all patients more than 18 years old with indication to IL-E and after informed consent signature were enrolled in this interventional, non-randomized, single-arm, prospective study. An ICG-FA was performed during the abdominal and thoracic stage, and data such as blood time of fluorescence appearing, speed of perfusion, quality of perfusion of the GC (good, poor, ischemic), blood pressure, heart-rate etc. was collected. Baseline clinical and demographic parameters, GC dimensions and other intraoperative parameters (inotropic drugs, fluid balance, etc.) were also gathered. In 4th post-operative day an x-rays Gastrographin swallow was always performed to detect the presence of an AL. AL development was registered and sorted following Clavien-Dindo and SISG severity classifications. Univariate analysis was done considering significant a 95% confidence level ($p<0.05$). Factors with $p<0.05$ were subjected to multivariate analysis.

RESULTS: A total of 100 patients were enrolled. Any degree of AL was observed in 32 patients. Subjective perfusion evaluation turned out a very specific test (94,1%) with a good negative predictive value (NPV 71,9%, p 0.034), but not powerful enough in detecting patients at risk of leak (sensibility 21,8%, PPV 63,6%). The GC perfusion speed (cm/sec) measured during the abdominal stage, after gastric vascular isolation and before tubulization, showed a statistically significant association with AL risk as a continuous variable (p 0.003). Similarly the median arterial blood pressure at the time of anastomosis during the thoracic stage (p 0.001) or the use of inotropic drugs (p 0.033) were significantly associated to AL development.

CONCLUSIONS: GC perfusion speed at ICG-FA is an objectively measurable parameter that could in future predict AL risk. Further studies to possibly identify a cut-off value are needed. Other results emphasize the importance of the microcirculation in the development of AL.

6. THE GENERATION AND VALIDATION OF FOUR NEW ESOPHAGEAL CANCER CELL LINES

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Background

Research into esophageal cancer, in particular adenocarcinoma, has been hampered by a paucity of relevant pre-clinical models. To date, only 13 bona fide adenocarcinoma cell lines have been published, with only six being derived from patients with confirmed Barrett's esophagus. Having so few available cell lines makes it difficult to model the genetic diversity observed in esophageal adenocarcinoma. In addition, only one of these lines has been shown to be reproducibly metastatic in xenograft models. This is in distinct contrast to the disease in the human, which is almost universally metastatic when left untreated.

Methods

Using our previously published intramuscular xenografting technique[1], patient derived tumour xenografts (PDTX) were generated from endoscopic biopsies of treatment naïve esophageal adenocarcinoma and SCC biopsies. Following successful engraftment, PDTX tissue was digested in order to generate small explant pieces. Explants were then plated with media and cultured for extended periods until a dominant clone was cultured. One cell line was directly obtained from the malignant ascites of a mouse that was harboring a PDTX that had metastasized. Established cell lines then underwent validation, which consisted of short tandem repeat (STR) analysis, targeted oncogene assessment using the Illumina TruSeq cancer panel, tumorigenic assay, assessment of chemotherapeutic response, immunohistochemical (IHC) analysis for both adenocarcinoma and SCC markers as well as FACS analysis for both epithelial and human markers.

Results

Matched PDTX and xenograft derived cell lines were generated from two separate SCCs in addition to two separate adenocarcinomas. From one of the adenocarcinoma lines, two separate cell lines were generated, with one clone demonstrating a reproducibly metastatic phenotype, while the other remained non-metastatic. STR analysis confirmed all of the PDTXs and cell lines were derived from their respective patients and IHC analysis confirmed that they expressed the appropriate epithelial markers. The cell lines also demonstrated the ability to form organoids when grown in 3D culture.

Conclusion

We have successfully generated and validated four additional esophageal cancer cell lines (two adenocarcinoma and two SCC) with matched PDTXs. The combination of both models creates a powerful tool, given the ability of PDTXs to recapitulate the heterogeneity and stromal elements of the original tumour, and the versatility of cell lines for mechanistic studies.

1. Read, M., et al. Annals of surgical oncology 2015. Disclosure All authors have declared no conflicts of interest.

7. A CHEMORADIOTHERAPY TREATMENT RESPONSE MRNA SIGNATURE AS PREDICTOR FOR ESOPHAGEAL ADENOCARCINOMA TREATED ACCORDING TO THE CROSS REGIMEN

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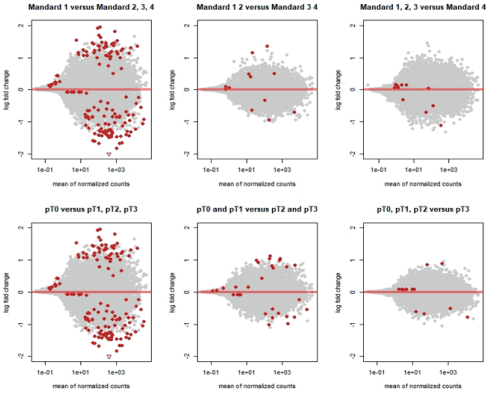
Despite advances in therapy, esophageal adenocarcinoma (EAC) remains a malignancy with poor prognosis. To improve patient outcome, it is imperative to improve treatment stratification and upfront patient selection. In the current study, the relation of mRNA expression profiles to pathological treatment response to preoperative chemoradiotherapy was investigated.

In this prospective observational study, EAC patients treated with chemoradiotherapy according to CROSS (carboplatin and paclitaxel) followed by surgery were included (1). A discovery cohort (n=44) was set up, containing RNA sequencing profiles of pre-treatment endoscopic tumor biopsies.

Patients were stratified in subgroups according to pathological response to the CROSS regimen as classified by the Mandard score and pathological T-stage (pT). Mandard 1 and pT0 depict a complete response to CROSS, whereas higher scores and stages are associated with incomplete response.

Differential expression analysis was performed to investigate the differences between the complete (n=6) and incomplete (n=38) responders (figure: differentially expressed genes in red). This resulted in 144 genes, collectively referred to as "complete response signature", which are important in immune system pathways. Using the 35 most statistically significant genes from this signature, we trained a model for prediction of complete response to CROSS therapy. This model has a sensitivity of 100% and a specificity of 89%.

Currently, a validation-cohort of CROSS treated EAC patients is being assembled, to validate the performance of our 35 gene prediction set. Application of this relatively small gene set will be more translatable to clinic and could be employed to improve treatment stratification of EAC patients.



8. MULTIMODAL THERAPY IN ESOPHAGEAL CANCER BEYOND CLINICAL TRIAL: SINGLE CENTRE EXPERIENCE

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Aim: investigate the factors influencing the choice of neoadjuvant treatment type in the real world, analyzing our single high-volume center experience.

Background & Methods: The neoadjuvant chemoradiotherapy is the standard of care for esophageal cancer [1- 2]. This consensus stems from the results of CCT performed on highly selected patients. However, the best treatment for non-selected patients remains unclear. In our clinical practice the treatment considered the goal standard is a TCF regimen with 50GyRT [3-4-5], which showed in our CCT an R0 resection rate of 88% and 5 y OS of 43%, better than CROSS trial. Despite these results, since 2012 not all patients underwent the same ideal treatment. We analyzed a real life patients group, that from the oncological point of view, they would be treated with our protocol in an intention to treat setting.

Results: From 2012 to 2017, 244 patients were treated. Analyzing retrospectively our data, it emerges that we have chosen the therapeutic strategy based on patient's characteristics: those aged over 75 yrs or with severe comorbidities were addressed to a "weakened" treatment: 37 with chemotherapy, 24 with radiotherapy and 55 with concomitant chemoradiotherapy different from our protocol. 125 with our protocol. Further selection involved lymph node status and patients with lymph node involvement (>N2) were referred to chemotherapy. The results confirmed that the protocol achieves better results in pathological response (pT0N0 in protocol 40,8% vs 18.2% in standard chemoradiotherapy – p value <0.001) and overall survival, especially for squamous hystotype. Regarding adenocarcinoma, chemotherapy and our protocol obtain good results for OS, although they differ on pathological response (pCR: 40.8% vs 5.4%). Most of the patients referred to chemotherapy had nodes involvement at the diagnosis (88.9%) and pathological response on nodes was significantly worse than protocol (pN0: 26.7% in chemotherapy vs 77.5%), however survival was similar between the two treatments.

Conclusion: Chemoradiotherapy is currently the gold standard of treatment for esophageal cancer but it cannot be consider the only treatment, especially for real life patients, less ideal but still requiring treatment. Clinical trials are certainly useful in providing information on highly selected patients, but clinical practice must consider patients whose conditions require tailored treatment.

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9. DIAPHRAGMATIC HERNIA AFTER IVOR-LEWIS OESOPHAGECTOMY: ANALYSIS OF RISK FACTORS AND SURGICAL REPAIR RESULTS

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OBJECTIVE: oesophagectomy is the mainstay of curative treatment for oesophageal cancer and post-oesophagectomy diaphragmatic hernia (PODH) represents a potentially life-threatening complication with an underestimated occurrence rate and unclear related risk factors. Aim of this study was to identify possible risk factors of PODH and results of surgical treatment from experience of two tertiary referral centers.

METHODS: all patients affected by a clinically resectable oesophageal cancer (any T, any N and M0) and submitted to Ivor-Lewis oesophagectomy, regardless of technique (open, hybrid or totally minimally invasive) between 1997 and 2017 at our Institutions were selected for this study. Demographic, clinical pre, intra, post-operative, and follow-up data were prospectively collected in an electronic database. A retrospective analysis was conducted in order to evaluate the incidence of PODH, associated risk factors and surgical repair results.

RESULTS: 414 patients underwent Ivor-Lewis oesophagectomy for cancer in the study period and 22 (5.3%) developed PODH at a median follow-up time of 16 months (6 - 177). Surgical repair was mainly conducted by laparoscopic approach (77%) with a conversion rate of 24%. Postoperative morbidity was 22.7% and mortality 4.5%. Median postoperative hospital stay was 6 days (2 - 95). 3 recurrences (13.6%) occurred at a median follow-up time of 10.1 months.

A wide univariate analysis identified statistically significant associations between PODH occurrence and the administration of preoperative chemoradiation, a complete pathological response (CPR) and a harvested lymph-nodes number (HLN) larger than 33 (p-value 0.016, 0.001 and 0.024 respectively). A significant association with a large HLN number was confirmed by the multivariable analysis (0.026) along with CPR which could however be considered as a longer survival-related bias.

CONCLUSIONS: The minimally invasive surgery and the neoadjuvant chemoradiation, in contrast to results of other authors, in our experience are not associated with PODH development, while a HLN number larger than 33 resulted to be an independent risk factor, probably mirroring the extent of surgical demolition in oesophagectomy. Surgical repair can be safely and effectively performed trough laparoscopy but recurrences can frequently occur.

NOTES

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