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CANCERS OF THE LOWER GI TRACT

BY DR. CRISTINA NADAL, BARCELONA, SPAIN

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Meeting Summary

BREAKOUT SESSIONS

The importance of recognizing Microsatellite instability tumors

Multiplex Approach to colon cancer testing: ready for the prime time?

THE IMPORTANCE OF RECOGNIZING MICROSATELLITE INSTABILITY TUMORS

Microsatellite Instability Screening

Dr. Kinga Stadler (MSKCC)

- dMMR testing should be done in all new diagnosed CRC or at least in all >70y and >70y fulfilling revised Bethesda Criteria
- Purposes:
  - Lynch syndrome diagnosis
  - Stage II good prognostic definition (no adjuvant therapies)
  - mCRC: immunotherapy trials

PD1 antibody for MSI High tumors

Dr. Dung Le (Sidney Kimmel Comprehensive Cancer Center)

- dMMR should be always tested
- dMMR tumors are highly responsive to checkpoint blockade with anti PD-1

MULTIPLEX APPROACH TO COLON CANCER TESTING: READY FOR THE PRIME TIME?

Dr. James Ford (Stanford University)

- Academic center experience: Stanford Cancer Genomic workflow
- MYPATHWAY Study (4 basket trials)
  - Hedgehog (Visnodegib)
  - BRAF (Vemurafenib)
  - EGFR (Erlotinib)
  - HER2 (Trastuzumab/Pertuzumab)
- Tumor heterogeneity
- Liquid Biopsies
- Molecular tumor Boards
- Bioinformatics, biostatisticians, reimbursement

GENERAL SESSION

Controversies in Surveillance after adenoma and CRC diagnosis

CONTROVERSIES IN SURVEILLANCE AFTER ADENOMA AND CRC DIAGNOSIS

Early detection of CRC neoplasia: Combination of 8 cancer associated blood-based protein biomarkers

Dr. Christensen

- CEA, AFP, hs-CRP, Ferritin, Galectin-3, CYFRA 21.1, CA 19.9, TIMP-1 (ARCHITECTURE machine by Abbott)
- Endpoints: Predict detection of CRC and high risk adenomas
- Reduced model performing also well

CRC Screening: global disparities in resources and approaches

Dr. Rabeneck (University of Toronto)

- Types of screening: FIT, sigmoidoscopy, Colonoscopy
- Colonoscopy is less effective in preventing death of proximal CRC (technique vs biology?)
- Better organized screening rather than opportunistic
- Differences among countries: when to start and how

CONTROVERSIES IN SURVEILLANCE AFTER ADENOMA AND CRC DIAGNOSIS

Controversies in Surveillance after adenoma and CRC diagnosis

Dr. Michael Bretthauer (University of Oslo)

- Currently finding more lesions than expected…surveillance is a challenge!
- Surveillance just on high-risk adenomas
- EPoS trials (European Polyp Surveillance)
- Surveillance after CRC: tests? How often?
- How to measure surveillance benefit? OS is not!!

CONTROVERSIES IN SURVEILLANCE AFTER ADENOMA AND CRC DIAGNOSIS

Novel endoscopic Screening approaches

Dr. Douglas Rex (Indiana University)

- Colonoscopy is operator dependant (variability)
- Paris classification, how to recognize flat and depressed lesions
- Trained endoscopist, meticulous technique, good preparation
- Adenoma detection rate (ADR) as surrogate of endoscopy quality
- Chromoendoscopy, high definition endoscopy, full spectrum endoscopy (FUSE), EndoCuff, EndoRing
- Measures to predict complete resection (specially in serrated) adenomas

CONTROVERSIES IN SURVEILLANCE AFTER ADENOMA AND CRC DIAGNOSIS

Complexities of Pathological assessment of adenomas and serrated polyps

Dr. Carolyn Compton (Mayo Clinic)

- Serrated adenomas (still largely unknown, not feared, not found, incomplete resection)
- 1/3 CRC generated through the serrated pathway (either MSI/MSS)
- Serrated morphology carcinoma with high RAS/BRAF mutations (bad Px)
- Hyperplastic serrated lesions (80-90%) vs serrated adenomas (Sessile Serrated Adenoma (SSA) (more mBRAF) & Traditional Serrated Adenoma (TSA) (more mRAS)
- Surveillance for SSA/TSA depends on number of lesions, size, side… (3 to 5 years); surveillance for hyperplastic lesions 5-10 years
- Mixed polyps (Serrated/Adenomatous)
- Serrated Polyposis Syndrome (SPS) definition (50% lifetime risk for CRC; annual surveillance recommendations; some surgical recommendations)

KEY NOTE LECTURES

Global Overview of CRC Past, Present and Future

GLOBAL OVERVIEW OF CRC
PAST, PRESENT AND FUTURE

Dr. David Cunningham (Royal Marsden)

- Substantial progress in CRC in the past 40 years
- Advances in diagnosis, surgery of primary and metastasis, loco regional treatments
- Adjuvant in stage II: high risk features (T4, EMVI, CDX-2 negative, poorly differentiated histology, <12 nodes examined) or less likely to benefit (>70y, MMR deficient, favourable genetic profile?, stem cell profile??)
- Incremental gain from 6 to 30 months in mOS
- Pembrolizumab as one of the more exciting drugs
- No biomarkers for chemotherapy/ antiangiogenic drugs
- antiEGFRs for 50% of RAS WT mCRC
- mBRAF at TRIBE study (FOLFOXIRI) nice responses but no differences in mOS
- Systemic treatment is not always the best option (f.e.: oligometastic disease)
- Multidisciplinary team, CLOCC study (RFA, impacting on OS)
- CRC molecular subtypes (collaborative aspect)
- Liquid biopsy: ctDNA (PROSPECT-C study as an example; detection of resistance; ctDNA in adjuvant setting)

GLOBAL OVERVIEW OF CRC
PAST, PRESENT AND FUTURE

Focus on rectal cancer

Dr. Daniel Haller (Abramson Cancer Center Pennsylvania)

- Changes in epidemiologic pattern (poor differentiated rectal cancer in younger)
- Endpoints in treatment of rectal cancer
- Risk stratification in rectal cancer patients (Gunderson review)
- Past 40 years hallmarks in rectal cancer:
  - Rapid globalization of neoadjuvant chemo radiation
  - Administration of radiotherapy: Short-course vs Long-course, chemo radiation vs radiation alone, all people need radiation therapy (?)
  - Surgery (TME, local excision, laparoscopic vs open), tumor board
  - Time of surgery: last
  - Always surgery or conservative?
  - Role of adjuvant?
  - Minimal impact on biologics in rectal cancer
  - Minimal progress in cytotoxic therapy in rectal cancer
  - Guidelines
  - Multidisciplinary tumor boards

GENERAL SESSION

Diverse International Perspectives on the Work-up and Management of Rectal Cancer

DIVERSE INTERNATIONAL PERSPECTIVES ON THE WORK-UP AND MANAGEMENT OF RECTAL CANCER

Endoscopic Ultrasonography vs MRI for Staging and Response Evaluation

Dr. Gina Brown (Royal Marsden)

- T3 rectal cancers (80%) sub classification (extramural spread is objectively)
- MERCURY trial: T1 to T3b (MRI good prognosis tumours) recurrence rates is very low; CRM involvement 20% recurrence
- Lymph node size in MRI does not correlate to pathology
- For low rectal cancers: CRM involvement by MRI
- pEMVI detection should be around 30% (high variability); stroger predictor for distant metastasis
- Assessing radiologic response by MRI: it is a continuum
- mrTRG assessment and OS: TRG 1-3 vs TRG 4-5 (better than pathology)
- TRIGGER trial (prospective phase III trial taking into account mrTRG for decisions vs not)

DIVERSE INTERNATIONAL PERSPECTIVES ON THE WORK-UP AND MANAGEMENT OF RECTAL CANCER

Short-course vs Long-Course Chemo radiation Therapy

Dr. Claus Roedel (university of Frankfurt)

- Short course radiotherapy (5x5 Gy) followed by surgery vs Chemoradiation followed by delayed surgery (Polish Trial and Trans Tasman Study): equal SP, LC, OS, late toxicity, less acute toxicity, less expensive, patient convenient, less downsizing, higher surgical morbidities, not safely combined with chemotherapy
- European guidelines: SCRT for intermediate stages
- NCCN 2016 guidelines allows short-course for T3 or N+, not for T4
- Stockholm III trial explored quick vs delayed TME showing delay is better
- Polish II trial
- RAPIDO trial
- TIMING trial
- German CAO/ARO/AIO-12 trials
- US Rectal Cancer Consortium

DIVERSE INTERNATIONAL PERSPECTIVES ON THE WORK-UP AND MANAGEMENT OF RECTAL CANCER

Surgical Options for low Rectal Cancer

Dr. Philip Paty (MSKCC)

- Tme
- Laparoscopic vs open surgery
- Local excisions
- Robotic surgery
- MSKCC experience
- OPRA Trial T3 and lower T2 (chemoradiation followed by FOLFOX/CapOX or reverse)

DIVERSE INTERNATIONAL PERSPECTIVES ON THE WORK-UP AND MANAGEMENT OF RECTAL CANCER

Chemotherapy for Rectal Cancer

Dr. Bengt Glimelius (Uppsala University)

- Concomitant to preoperative radiotherapy
  - 5FU/capecitabine are the standard
  - Sequentially
  - Substitution
- Adjuvant: a lot of controversy

ORAL ABSTRACT SESSION

Cancers of the colon, rectum and anus

CANCERS OF THE COLON, RECTUM AND ANUS

Neoadjuvant chemoradiation for fixed cT3 or cT4 rectal cancer: Results of Polish II multicenter phase III trial

Dr. Krzystof Bujko

- Chemoradiation with oxaliplatin vs SCRT followed by chemotherapy with oxaliplatin
- 540 patients
- Main endpoint R0 resection equal;
- pCR equal
- No differences in late toxicity (dose reduction similar)
- No differences in postoperative complications
- DFS, local failure, and OS similar

- Lower acute toxicity and trends to better OS favour SCRT-chemotherapy

CANCERS OF THE COLON, RECTUM AND ANUS

ACCORD12/0405-Prodige 2 phase III trial neoadjuvant treatment in rectal cancer: results after 5 years of follow-up

Dr. Eric Francois

- Capecitabine-RDT(45) vs CapOX-RDT (50)
- Primary endpoint pCR: negative
- No differences on R0 resection, DFS, OS, LR
- No differences in toxicities , QoL
- Dworak score, age >70 and ypN as prognostic items for OS and DFS
- Concordant with NSABP R-04 trial
- No information about adjuvant treatments and treatments after recurrence

- Oxaliplatin is more toxic, no more pCR, no improvement of OS, LR, DFS

CANCERS OF THE COLON, RECTUM AND ANUS

The incidence of secondary pelvic tumors after previous (chemo)radiation for rectal cancer

Dr. Anouk Rombouts

- Netherland registry (1989-2007)
- Median follow-up of 6 years
- All pelvic tumors considered
- 29.214 patients (approx. half received RDT and half not)
- Second tumors: RDT (+) 11.1 vs RDT (-) 14.2%
- Compared to Dutch registry
- Second tumors more frequent after postoperative RT compared to preoperative

- No increase of second tumors after rectal cancer radiotherapy
- Radiotherapy reduces the risk for pelvic tumors (0.78) - protective effect (specially for prostate cancer)

CANCERS OF THE COLON, RECTUM AND ANUS

ORR in STEAM, a randomized, open-label, phase 2 trial of sequential and concurrent FOLFOXIRI-bevacizumab vs FOLFOX-bevacizumab for 1st-line treatment of mCRC

Dr. Johanna Bendell

- **Like TRIBE**
- **280 patients**
- **4 months induction and maintenance (5FU/capecitabin bev)**
- 3 arms (FOLFOXIRI+Bev concurrent, sequential, FOFOX6+Bev)
- Primary endpoints: ORR1 and PFS1
- ORR1 better for FOLFOXIRI+Bev (60 vs 40)
- Better PFS
- Higher resection rate (12 vs 8)
- More toxicity in the combination (diarrea, neutropenia)
- More hypertension in concurrent FOLFOXIRI+Bevacizumab

CANCERS OF THE COLON, RECTUM AND ANUS

MAVERICC, a phase 2 study of mFOLFOX6-Bevacizumab vs FOLFIRI-Bevacizumab with Biomarker stratification as 1st-line therapy in mCRC

Dr. Heinz-Josef Lenz

- Safety and tolerability
- High ERCC1 correlates to bad prognosis
- Plasma VEGF
- 376 patients (ERCC1 stratification)
- Endpoint: ERCC1 correlates to PFS
- Endpoint: VEGF biomarker for response
- No significant differences in PFS and OS
- PFS by ECRR1 levels (high vs low) did not show significant differences

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