12th Central European Oncology Congress

A Best of ASCO® Meeting

June 22-25, 2016

HOTEL KVARNER
OPATIJA, CROATIA

BOOK OF ABSTRACTS

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BEST OF ASCO®

2016 ANNUAL MEETING

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TECHNICAL ORGANIZER

PENTA Ltd.
Contact person: Ana Jurašić
Address: Izidora Krsnjavoga 25, 10000 Zagreb-HR
Phone: +385 1 4628 615, +385 1 4553 290
Cell phone: +385 91 4553 200
Fax: + 385 1 4553 284
E-mail: ana.jurasic@penta-zagreb.hr

Contents

Dear colleagues, dear friends,

We are announcing the 12th Central European Oncology Congress, Croatian Society of Oncology's Best of ASCO® Conference, a program licensed by the American Society of Clinical Oncology, which will be held at the Hotel Kvarner, Opatija, Croatia on June 22-25, 2016.

The Central European Oncology Congress is a regional, multinational meeting intended for the continuing education of medical, radiation and surgical oncologists, other health professionals involved in cancer patient care and trainees.

CEOC-2016 combines Best of ASCO® presentations, multidisciplinary tumor boards, a forum for young oncologists, and satellite symposia by pharmaceutical companies.

Poster presentations of clinical research results are invited. Brief oral presentations by selected poster presenters will be held and discussed with a panel of members of the Scientific Advisory Committee.

Please mark your calendars, save the date for CEOC-2016, and don't forget to register early for this sixt Best of ASCO® in Croatia! We are delighted that ASCO has again awarded us Best of ASCO® sponsored status, enabling us to give in depth reviews of the latest data presented in Chicago two weeks before our CEOC-2016. This is a great educational opportunity for all oncologists in Central and Eastern Europe who will be unable to attend the ASCO annual meeting.

Welcome!

On behalf of the Organizing Committee

Prof.dr.sc. Branimir I. Sikic
Stanford University
Stanford California, USA

Prof.dr.sc. Eduard Vrdoljak
Clinical Hospital Center Split
Split, Croatia

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Scientific Program:

Tumor Boards

Lung Cancers Tumor Board - 2016

SESSION CHAIR: Robert Pirker, MD, Medical University of Vienna, Austria

Cases by Prof. David Gandara, UC, Davis School of Medicine, Sacramento, California, USA

Faculty Panel

Medical Oncologists:

David Gandara (USA),

Dragana Jovanović (Serbia),

Miroslav Samaržija (Croatia)

Radiation Oncologists:

Jacek Jassem (Poland),

Antonio Juretić (Croatia)

Surgical Oncologists:

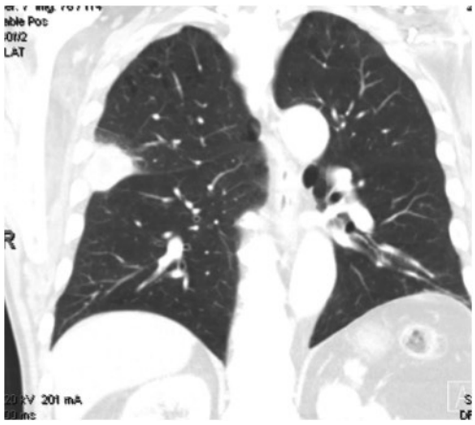
Tomaž Stupnik (Slovenia)

Case 1: CEOC Lung 2016

- 54 year-old man presents for routine physical. PMH remarkable for high blood pressure.
- 50 pack-year tobacco history, quit 10 years ago.

Question 1: The patient asks about lung cancer screening. You recommend:

1. No screening test
2. Routine CXR
3. Low dose non-contrast CT Chest
4. PET-CT scan
5. Screening lab for Carcinoembryonic Antigen (CEA)



- The patient has a screening CT showing a 4.1 cm right upper lobe mass. No lymph nodes are enlarged.
- Biopsy of the lesion shows adenocarcinoma, TTF1+.
- PET CT shows the FDG avid mass (SUV 7.5) and no other sites of disease.
- Pulmonary function tests are adequate for surgery.

Question 2: How would you stage the mediastinum in this case?

1. Yes, Endobronchial Ultrasound and Biopsy
2. Yes, Mediastinoscopy
3. No (mediastinal lymphadenectomy at lobectomy)

- The patient has a VATS lobectomy of the RUL with intraoperative mediastinal LN dissection at time of lobectomy. Pathology: 4.1 cm poorly differentiated adenocarcinoma. Margins are negative.
- 12 sampled hilar and mediastinal LN are negative for cancer.
- The patient recovers well from surgery.
- You Stage the patient as Stage IB (T2aN0M0) by 7th AJCC Staging System

Question 3: Would you offer platinum-based adjuvant chemotherapy to this patient - Stage IB (T2aN0M0) with a 4.1 cm primary tumor?

1. Yes
2. No

Question 4: If you choose to give chemotherapy, which chemotherapy regimen would you recommend for this Stage IB (T2aN0M0) adenocarcinoma patient?

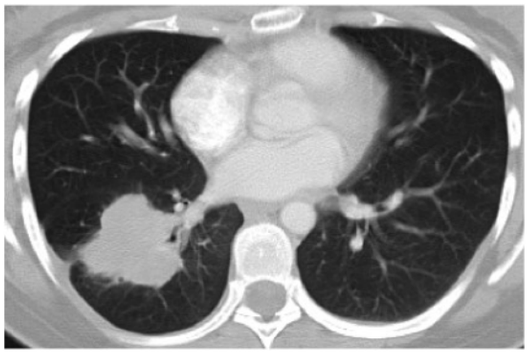
1. No adjuvant chemotherapy
2. Carboplatin-Paclitaxel-Bevacizumab
3. Carboplatin-Paclitaxel
4. Cisplatin-Docetaxel
5. Cisplatin-Pemetrexed
6. Cisplatin-Vinorelbine

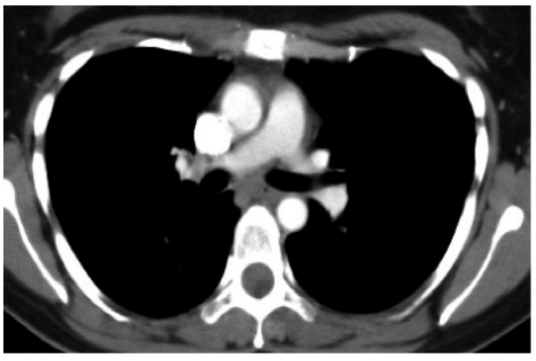
Take Home Points

- The NLST, which randomly assigned individuals with high-risk disease to three annual helical CT scans or chest x-rays, demonstrated a 20% reduction in lung cancer mortality and a 6.7% relative reduction in all-cause mortality.
- Adjuvant post-operative cisplatin-based chemotherapy improves survival in Stage II-III NSCLC, but is controversial in Stage IB and contraindicated in Stage IA.
- Carboplatin should not be substituted for cisplatin in the curative adjuvant setting, unless the patient has a contraindication to cisplatin.

Case 2: CEOC Lung 2016

- A 40 year old women with a distant 5 pack-year smoking history presents with cough and dyspnea.
- Chest x-ray that revealed a RUL mass.
- **PET-CT**: a 5.7 cm FDG avid right lung mass (SUV 15.3). Also 1.2 cm subcarinal level 7 lymph node with an SUV of 15.1.
- Brain MRI was negative for metastatic disease.
- Biopsy of RUL mass shows lung adenocarcinoma (CK7+, CK20-, TTF1+)





You biopsy the **subcarinal node** by EBUS, which is positive for lung adenocarcinoma.

The patient now is staged as IIIA (T2N2M0) Lung adenocarcinoma.

Question 1: You recommend:

1. Concurrent chemoradiation
2. Concurrent chemoradiation followed by RLL lobectomy (trimodality therapy)
3. Induction chemotherapy followed by surgical resection
4. Surgery followed by adjuvant chemotherapy and post-operative radiotherapy.

You decide to treat with pre-operative chemotherapy (cisplatin/docetaxel), and also to order molecular testing due to distant light smoking history in a young women with Stage IIIA cancer.

Question 2: You order molecular testing. Which do you choose?

1. EGFR mutation (by sensitive PCR method) & ALK rearrangement & ROS1 rearrangement (by FISH)
2. Next generation sequencing (NGS) for 300 genes, which includes EGFR mutation & ALK & ROS1 rearrangements

The patient proceeds with pre-operative cisplatin/docetaxel.

Repeat PET/CT scan after 2 cycles of chemotherapy shows shrinkage of lung mass and lymph node but **a new FDG avid lytic lesion of the pelvis**. Bone biopsy is positive for lung adenocarcinoma.

In the meantime, **molecular testing shows EGFR mutation (E19del)**.

Question 3: You recommend

1. **Add radiation to chemotherapy**, including thoracic + pelvic RT.
2. **Add radiation to chemotherapy**, including thoracic + pelvic RT, **followed by erlotinib afterwards**.
3. Stop chemotherapy and **start an EGFR-TKI** for oligo-metastatic disease, **together with radiation to the pelvic lesion**.

You decide to stop chemotherapy and begin an **EGFR TKI + pelvic RT** for oligo-metastatic disease.

Question 4: Which EGFR TKI would you select for this patient with a tumor positive for an EGFR Exon 19 deletion mutation? You recommend:

1. Afatinib
2. Erlotinib
3. Erlotinib and bevacizumab
4. Gefitinib
5. Osimertinib (AZD9291)

The patient is started on afatinib + pelvic RT, with a **superb response** (marked reduction in primary and resolution of subcarinal LN and

FDG avidity of the sacral lesion.

Question 5: You recommend

1. Continuing afatinib given the excellent response.
2. Proceed to lobectomy considering the patient has oligometastatic disease only.

The patient continues on afatinib alone. Fourteen months later she develops bone pain and has progressive disease in multiple sites.

Question 6: You recommend:

1. Platinum-based chemotherapy
2. Repeat tissue biopsy to examine resistance mechanism of EGFR-TKI
3. “Liquid biopsy” for cell free DNA to examine resistance mechanism of EGFR-TKI

The patient has a repeat tissue biopsy. Molecular testing shows an acquired EGFR-T790M resistance mutation

Question 7: You next recommend:

1. Platinum-based chemotherapy

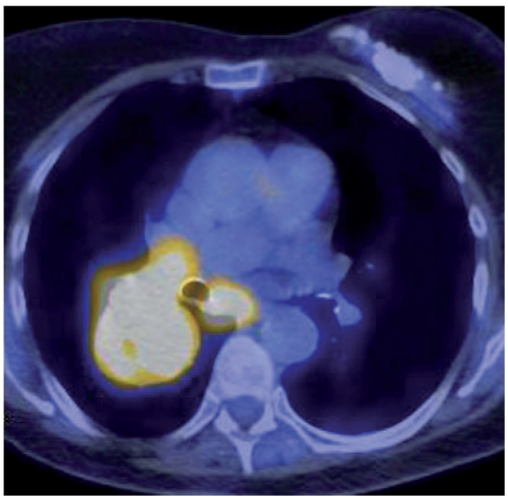
2. Osimertinib (AZD9291)

3. Afatinib and Cetuximab

Take Home Points

- Treatment for Stage IIIA NSCLC with single N2 LN may be individualized by patient characteristics. Options include pre-operative chemotherapy, pre-operative chemoradiation, concurrent chemoradiation or in some cases, surgery followed by adjuvant therapy.
- Lung adenocarcinoma harboring the E19del mutation is usually highly senstive to EGFR TKIs, and afatinib may be optimal.
- Local therapy for oligometastatic disease combined with TKI is a potential treatment option in EGFR and ALK rearranged NSCLC.
- At the time of recurrence after a 1st-2nd generation EGFR TKI, tissue and/or liquid biopsy is recommended to determine the mechanism of resistance and optimal therapeutic options.
- The 3rd generation EGFR TKI Osimertinib is now approved for T790M+ recurrent disease and is highly active in this setting.

Case 3: CEOC Lung 2016



56 year-old woman with 50 pack-year smoking history
Presents with cough and fatigue. ECOG PS 1.

PET/CT: RUL hilar mass with metastases to lymph nodes and bones.

Biopsy: **NSCLC-squamous histology.**

MRI of brain negative.

Question 1: For initial treatment of this patient with squamous NSCLC, you recommend?

1. Carboplatin and pemetrexed
2. Cisplatin and gemcitabine and necitumumab
3. Carboplatin and pemetrexed and bevacizumab
4. Carboplatin and paclitaxel and bevacizumab
5. Cisplatin or Carboplatin and gemcitabine

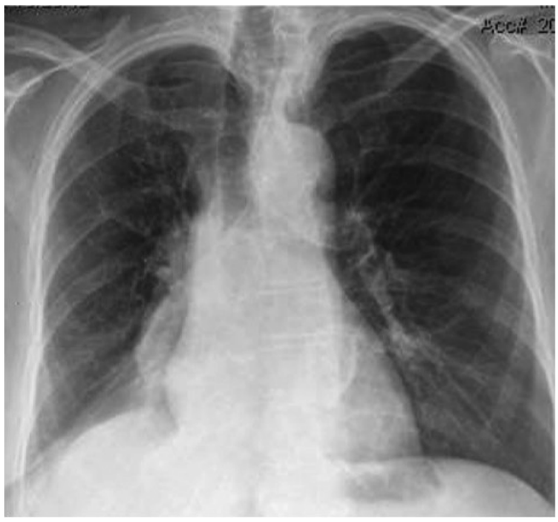
The patient is treated with **cisplatin-gemcitabine + necitumumab**.

PET CT after 2 cycles shows an excellent response.

However, after r**epeat scan after 4 cycles shows progressive disease**.
The patient is still Zubrod PS 1.

Question 2: You recommend:

1. Nivolumab without sending for PD-L1 testing.
2. Nivolumab only if PD-L1 testing is positive (>1%)
3. Pembrolizumab if PD-L1 positive (>1%)
4. Docetaxel and ramucirumab
5. Docetaxel alone



The patient receives nivolumab. She has a near complete response that is maintained for 6 months.

At that time, she develops **copious watery diarrhea** (grade 3) with incontinence and requiring IV hydration. Stool cultures are negative including c. diff.

Question 3: A CT abdomen is consistent with diffuse colitis. You next recommend?

1. Corticosteroids and loperamide
2. Colonoscopy
3. Empiric antibiotics
4. Loperamide

You initiate corticosteroids and slowly taper. Her diarrhea resolves quickly over a period of 2 weeks and you see her in clinic 4 weeks after onset.

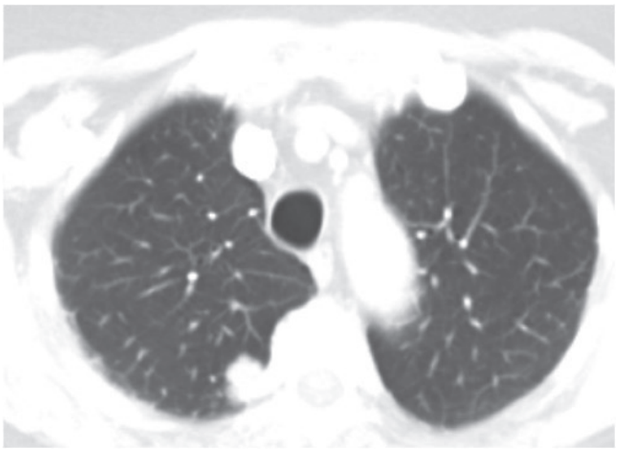
Question 4: Do you re-challenge with nivolumab?

1. Yes
2. No

Take Home Points

- Cisplatin/Gemcitabine + the EGFR MoAB Necitumumab is now an option for 1st line therapy of advanced Squamous NSCLC.
- Ramucirumab + docetaxel improves survival compared to docetaxel alone in 2nd line therapy of adenocarcinoma & squamous histology NSCLC.
- PD1 blockade with nivolumab or pembrolizumab improves overall survival compared to the standard 2nd line chemotherapeutic agent docetaxel.
- Immune related adverse events from PD-1 blockade are highly variable, often are responsive to immunosuppression, and occasionally fatal.

Case 4: CEOC Lung 2016



- A 70 year-old woman with an 80 pack-year smoking history presents with non-productive cough.
- CT Chest shows a right upper lung mass.
- Biopsy of the lung mass shows **small cell lung cancer (+synaptophysin &chromogranin)**
- PET CT shows that the RUL mass is FDG avid. No other sites of metastatic disease are noted.
- MRI brain is without intracranial metastases.

You stage the patient as Stage IA (T1aN0M0) (Limited Stage) Small Cell Lung Cancer. She has an excellent performance status and PFTs are adequate for surgery.

Question 1: You recommend

1. Cisplatin and etoposide with concurrent radiation
2. VATS Lobectomy with mediastinal lymph node sampling at time of lobectomy
3. Staged mediastinoscopy followed by lobectomy if lymph nodes negative for cancer

Mediastinal lymph node sampling is negative for malignancy.

- VATS lobectomy of right upper lobe shows 2 cm small cell lung cancer. Lymph nodes and margins are negative.
- She recovers well from surgery.

Question 2: You next recommend to the patient:

1. 4 cycles of adjuvant cisplatin and etoposide
2. Adjuvant cisplatin and etoposide with concurrent thoracic radiotherapy to mediastinum
3. Adjuvant cisplatin and etoposide followed by PCI
4. Adjuvant cisplatin and etoposide with concurrent thoracic radiotherapy to mediastinum followed by PCI
5. Observation only

Take Home Points

- Small cell lung cancer (SCLC) typcially presents as a central mass with associated mediastinal LNs and often metastatic disease.
- However, in carefully staged Stage I SCLC surgical resection, combined with post-operative adjuvant chemotherapy, may provide long-term survival.
- PCI reduces brain metastases and improves survival in limited & selected extensive stage SCLC cases

Gastrointestinal Cancers Tumor Board - 2016
Gastric / Pancreas / Neuroendocrine / Colon

SESSION CHAIR: Prof.Dr. György Bodoky, St. László Hospital,Budapest, Hungary

Cases by Prof. George A. Fisher, MD, Ph.D., Stanford University School of Medicine, Stanford, California, USA

Faculty Panel

Medical Oncologists:

Gyorgy Bodoky (Hungary),

Stjepko Pleština (Croatia)

Radiation Oncologists:

Antonio Juretić (Croatia)

Surgical Oncologists:

Marko Zelić (Croatia)

Case 1: CEOC Gastrointestinal 2016

34 yo lawyer with 30 lb weight loss

- 3-6 months early satiety
- EGD: ulcerated lesion in antrum
    - Bx: poorly differentiated adenoca with signet ring features
    - Her 2 neu (-)
- CT: thickened gastric wall; no enlarged nodes or mets

Your next step:

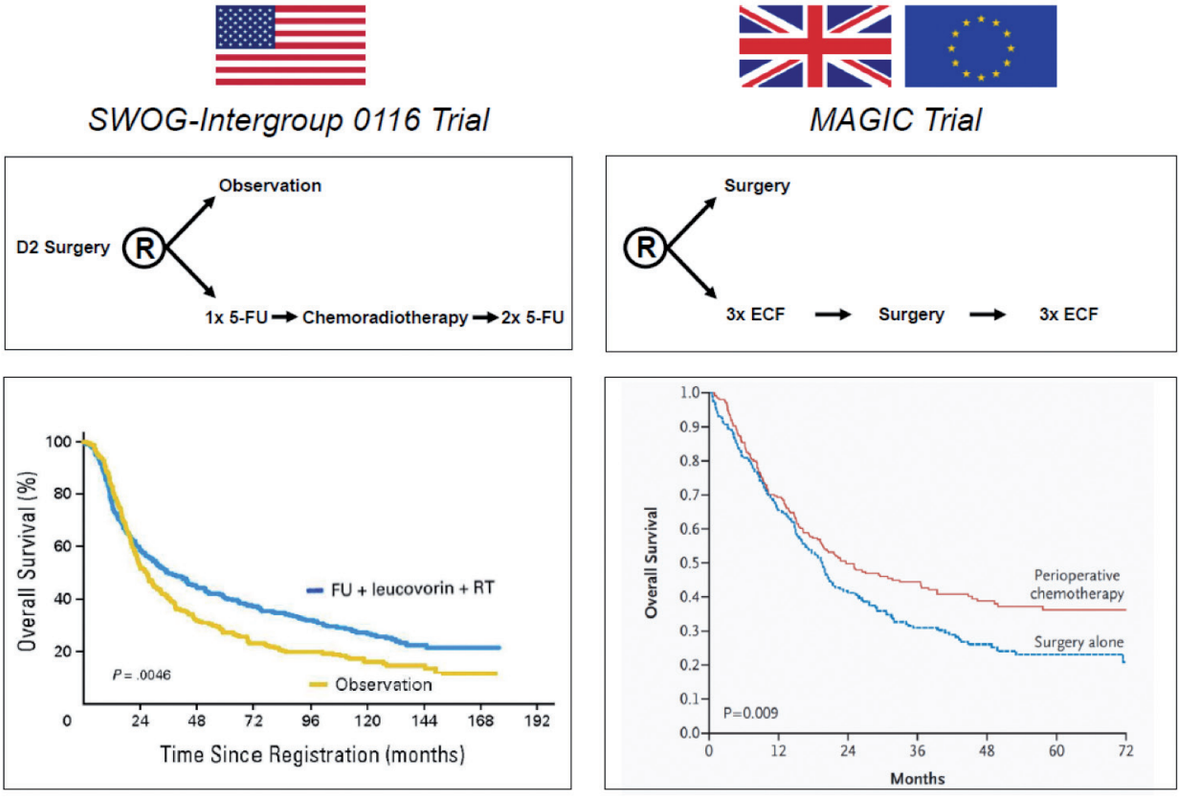
A. ECF (or EOX) x 3 f/b resection f/b same chemo x 3

B. FOLFOX (or your favorite fluoropyrimidine/platinum) f/b resection f/b same chemo

C. Chemoradiation with carbo-taxol f/b surgery

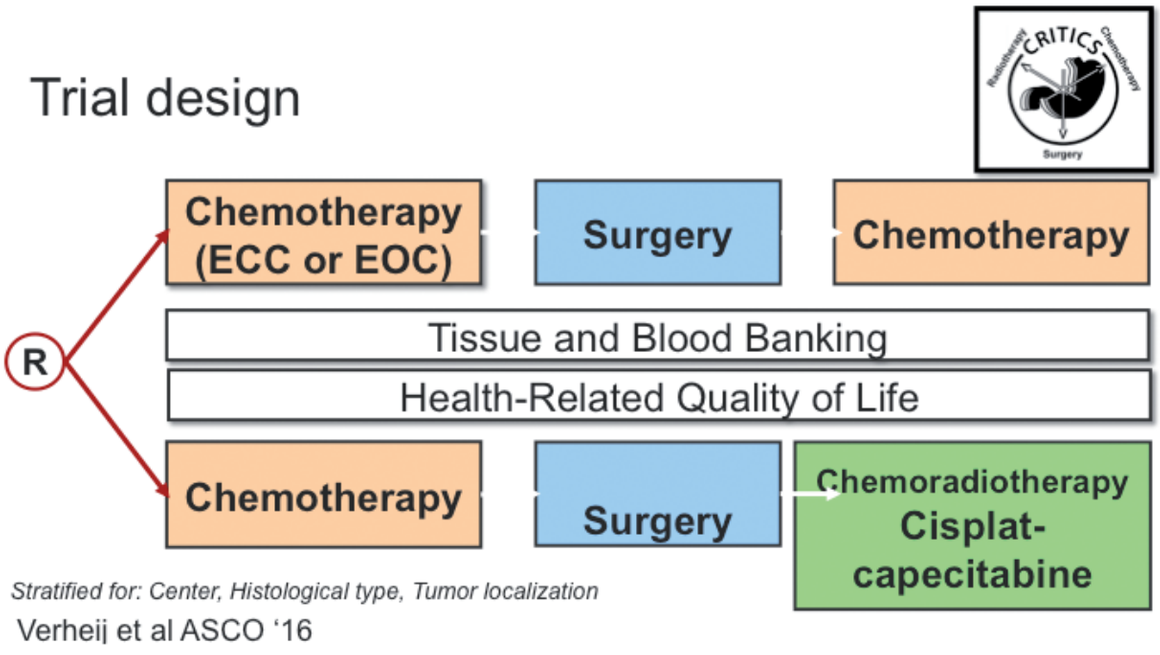
D. Gastrectomy with D2 node resection f/b chemoradiation

F. Gastrectomy with D2 node resection f/b chemo



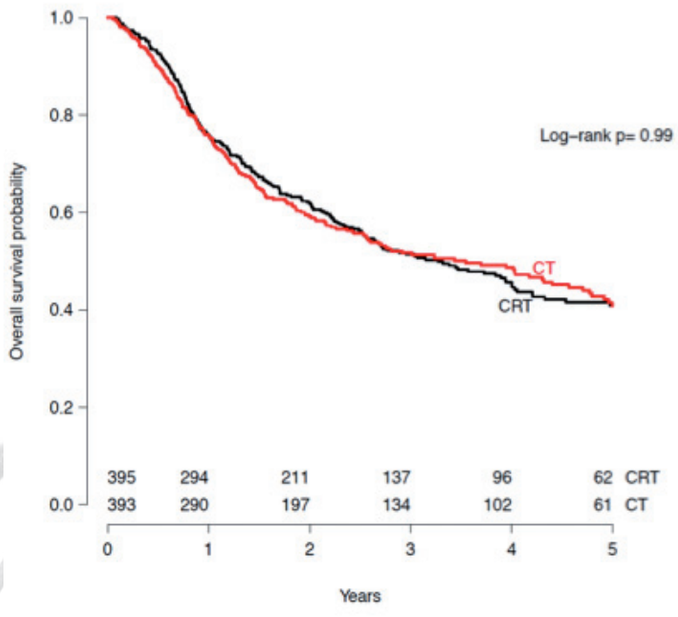
Macdonald et al. NEJM 2001; Smalley et al. JCO 2012
Cunningham et al. NEJM 2006

CRITICS: Trial design



Verheij et al ASCO '16

CRITICS: Overall Survival



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

Verheij et al ASCO '16

Father and paternal uncle gastric cancer at 50 and 33; Mother breast cancer at 48; you now order:

A. Blood for CDH1 gene mutation

B. Blood for BRCA1/BRCA2

C. IHC of tumor for mismatch repair proteins

D. A and C

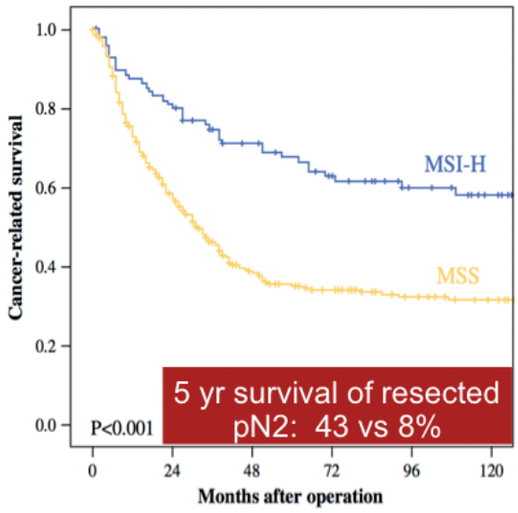
E. DNA sequencing / molecular profiling of tumor biopsy

F. All of the above

MSI and gastric cancers

- 10-25% of gastric cancers have MSI
- Majority due to MLH1 hypermethylation

	MSI	MSS
N =	111	361
Poorly D	43%	30%
Signet	21%	33%
Stage IV	8%	21%



Marrelli, D. et al Annals of Surgical Oncology 2015

He gets chemo (FOLFOX), surgery, chemoand 1 year later has liver metastases

A. Taxol

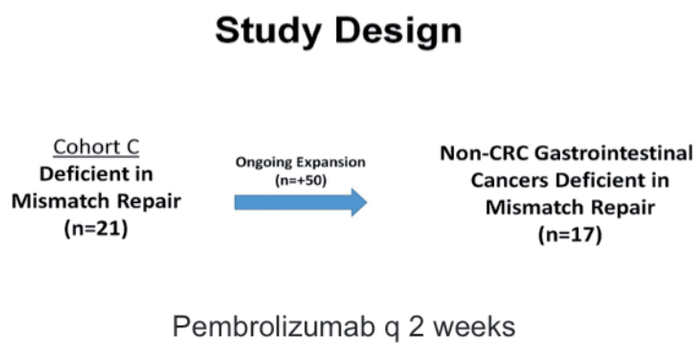
B. Ramicurumab

C. Taxol + Ramicurumab

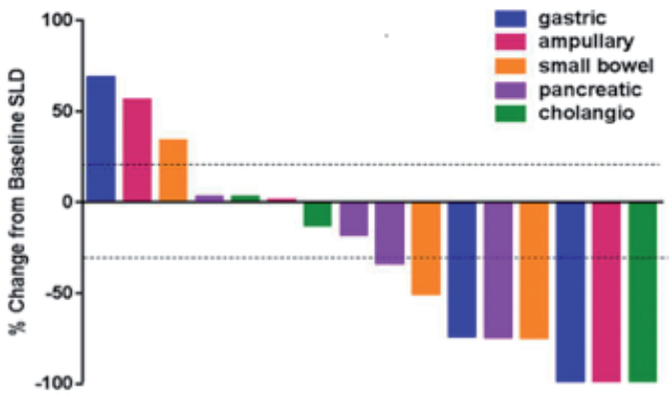
D. Your favorite platinum-fluoropyrimidine doublet

E. DFOX (docetaxel, 5FU, oxaliplatin)

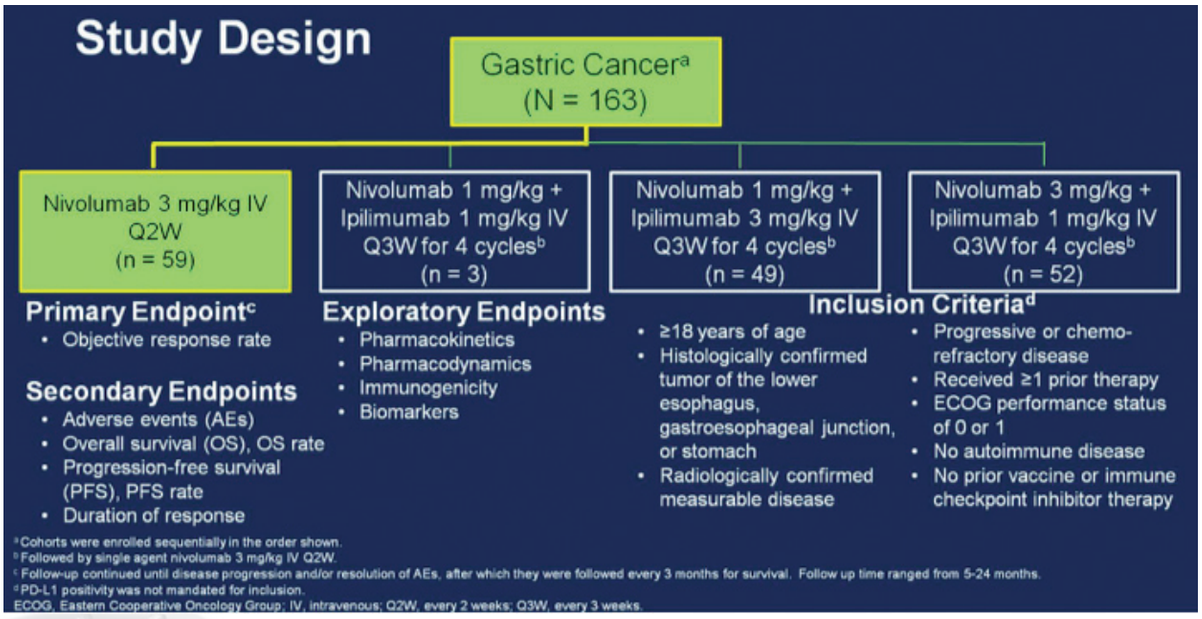
PD1 antibodies in MSI non-colorectal cancer:

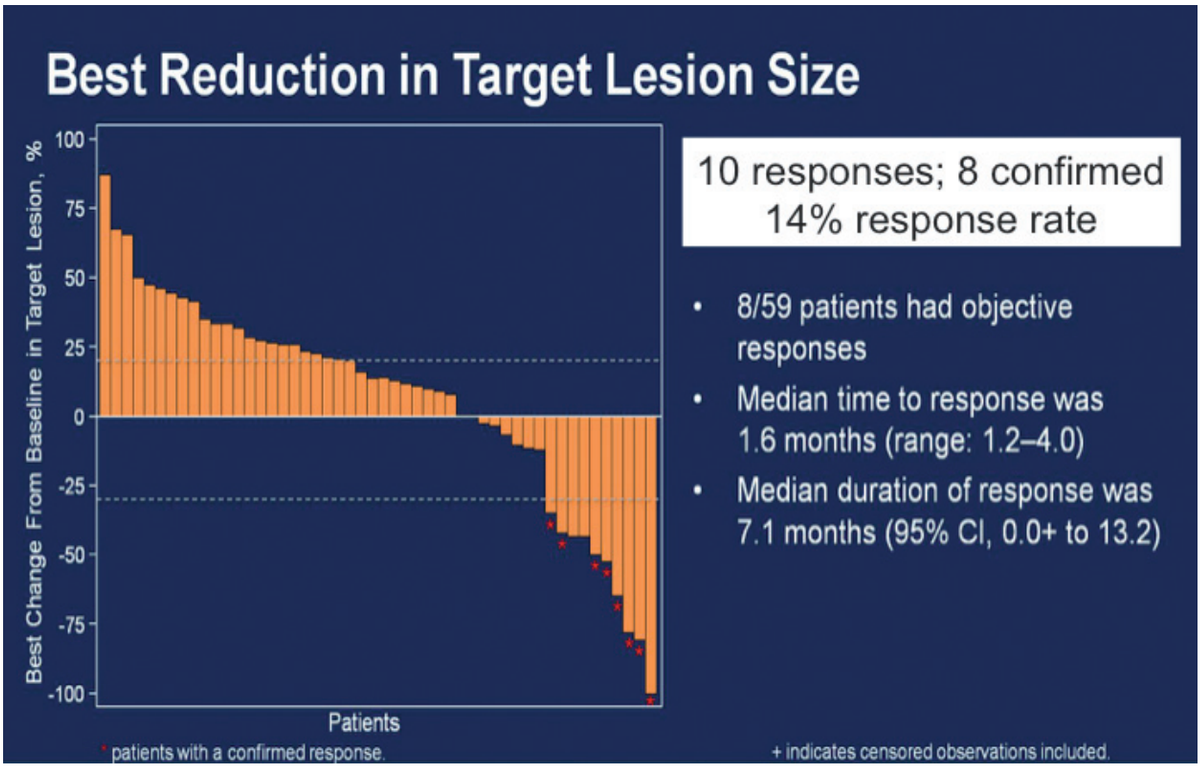


PD1 antibodies in MSI non-colorectal cancer:



PD1 antibodies in gastric cancer:





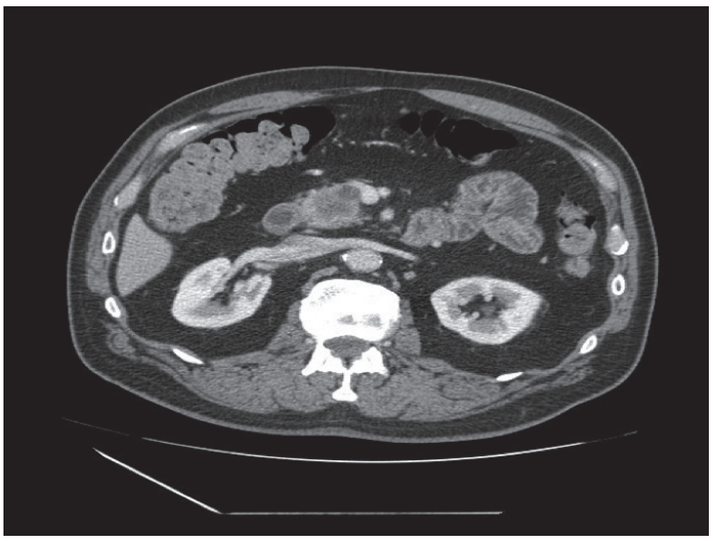
Take Home Points

- Value of both epirubicin and radiation questionable in resectable disease (Korean trial pending in node (+) pts)
- Her 2 neu is only validated marker for which we have an effective drug (10-15% false negative on "outside" path)
- MSI worth exploring if PD1-PDL1 antibodies "available"
    - Prognostic in resected disease (much like stage II colon)
    - Clinically impressive responses to anti-PD1 antibodies
- Encouraging response rates of unselected patients to PD1
    - Though response rates do correlate with PD-L1 (+) expression
    - Not yet clear if responses correlate with MSI

Case 2: CEOC Gastrointestinal 2016

52 yo with abdominal pain and jaundice

- 6 months prior to presentation: new onset diabetes
- Now with 10 lb weight loss
- T bili 6.4; alk phos 624; CA19-9 444
- Pancreatic protocol CT: dilation of biliary and pancreatic ducts; mass in head of pancreas



Your next step:

A. ERCP with stent placement

B. EUS with biopsy

C. PET CT

D. Whipple

E. A and B above

Stent placed; FNA: adenoca; CA19-9 declines to 120 with normalization of T bili

Was stent placement necessary?

You now offer:

A. Whipple

B. FOLFIRINOX

C. Gemcitabine / nab-paclitaxel

D. radiation (IMRT) with concurrent fluoropyrimidine

E. FOLFIRINOX x 4 f/b radiation (SBRT)

Whipple with vein graft: 4 cm mod diff adenoca; 3/12 nodes (+); perineural invasion; margins (-)

You now offer adjuvant:

A. gemcitabine

B. gemcitabine + capecitabine

C. gemcitabine f/b 5-FU / radiation

D. gemcitabine + nab-paclitaxel

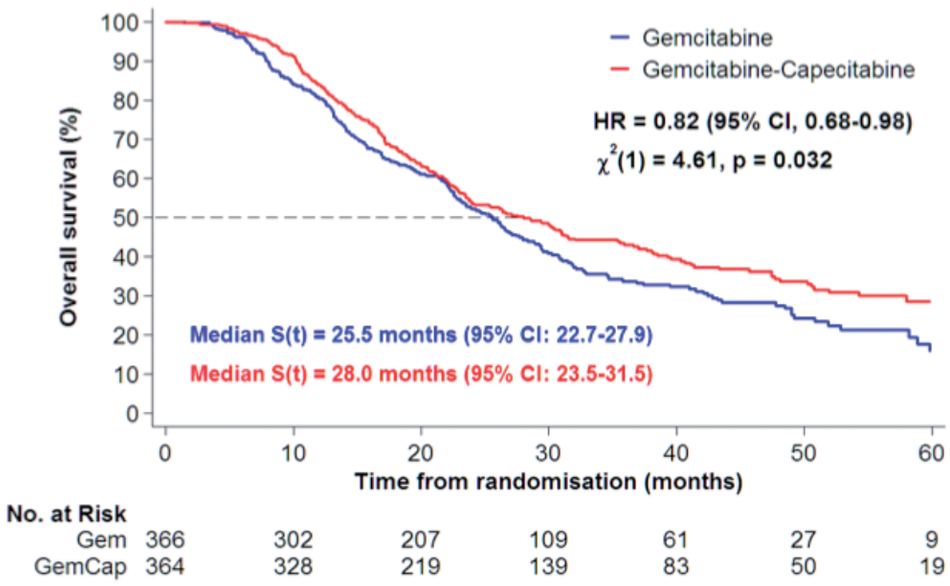
E. FOLFIRINOX

Evolution of Adjuvant Therapy for Pancreas

- [1]GITSG: 5-FU + XRT > Observation
- [2]CONKO-001: Gem > Observation
- [3]ESPAC-1: 5-FU > no chemo; no XRT > XRT
- [4]ESPAC-3: Gem = 5-FU
- [5]ESPAC-4: Gem + capecitabine > Gem
- [6]RTOG 9704: Gem or 5-FU – (5-FU + XRT) – Gem or 5-FU
- [7]JASPAC 01: S1 >> Gemcitabine

[1]Kalser et al. Arch Surg 1985; [2]Oettle H et al. JAMA 2007; [3]Neoptolemos JP et al. NEJM 2004; [4]Neoptolemos JP et al. JAMA 2009; [5]Neoptolemos et al ASCO '16; [6]Regine WF et al. JAMA 2008; [7]Uesaka, K. et al Abstr #145; GI ASCO '13;

ESPAC-4: Gem +/- Capecitabine



Recently completed / ongoing adjuvant trials

- RTOG 0848: gem +/- (5-FU radiation) [+/- erlotinib]
- NEOPAC: adjuvant gem +/- NEO-adjuvant gem/oxaliplatin
- SWOG: Neoadjuvant gem/nabpaclitaxel vs FOLFIRINOX
- APACT: gem vs gem + nab-paclitaxel
- PRODIGE 24: gem vs mFOLFIRINOX
- NLG0405: gem (or gem + 5-FU/XRT) +/- Algenpantucel
- Negative Trial

Gemcitabine x 4 months f/b 5FU+ radiationDisease free for two years, then two liver mets

Performance status excellent; CA19-9 350; LFT's normal

A. Biopsy liver met for confirmation and molecular profiling

B. PET scan and if (-) elsewhere, resect liver mets

C. SBRT to liver mets

D. gemcitabine + nabpaclitaxel

E. FOLFIRINOX

Gemcitabine + nab-paclitaxel with initial response but progression after 6 months

Performance status ECOG 1; now 5 liver lesions and no extra-hepatic disease; LFTs normal.

You now offer:

A. FOLFIRINOX

B. FOLFOX (or CAPOX)

C. FOLFIRI

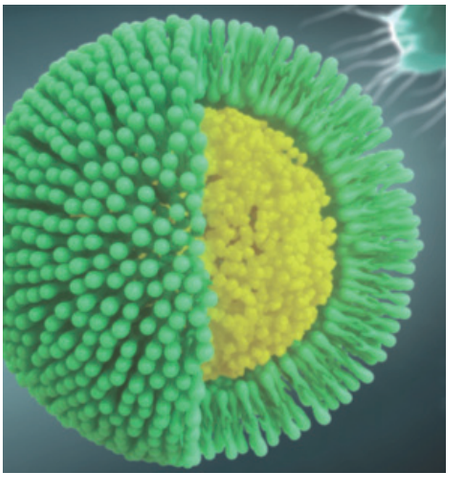
D. 5FU + liposomal irinotecan (MM-398)

E. Liver directed therapy (Radio or chemo embolization)

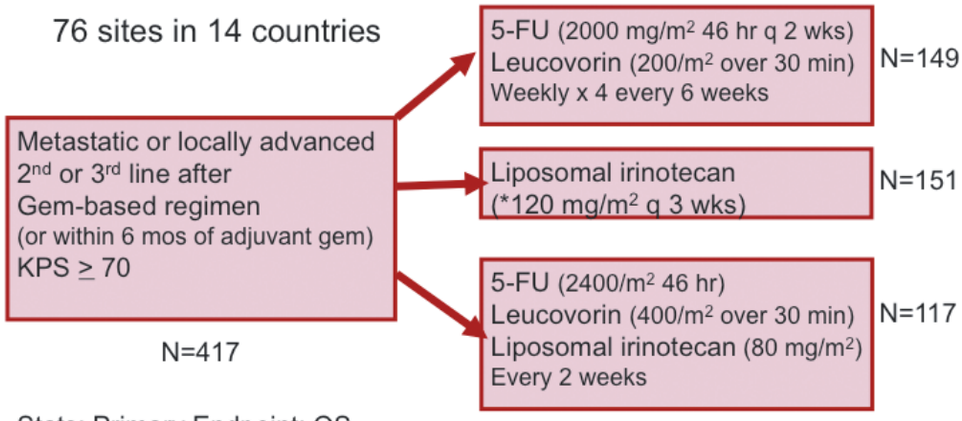
Nanoliposomal irinotecan (MM398)

Altered pharmacokinetics:

- prolongs half-life of irinotecan
- prolongs half-life of active metabolite, SN38
- increases intra-tumoral levels of both irinotecan and SN38



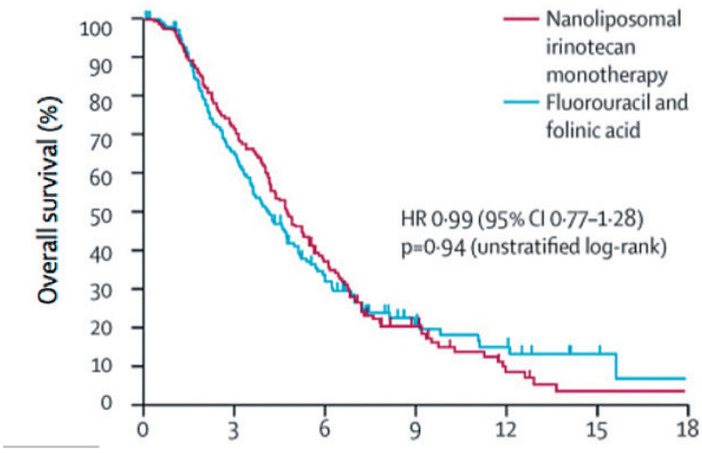
NAPOLI-1: 5-FU v MM398 v 5-FU+MM398



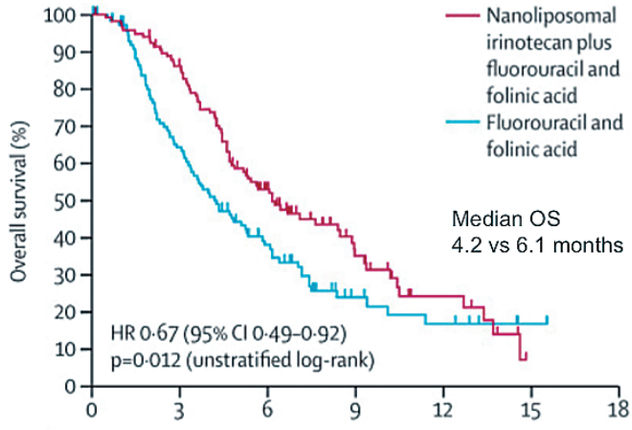
Stats: Primary Endpoint: OS
405 pts to have 98% power to detect HR 0.5
and 85% power to detect HR 0.67
Stratification: albumin, KPS, ethnicity

*Reduced by 20 mg/m2 for
homozygous UGT1A1*28 allele

Overall Survival: 5FU v liposomal irinotecan



NAPOLI-1 Overall Survival:5-FU v Liposomal irinotecan

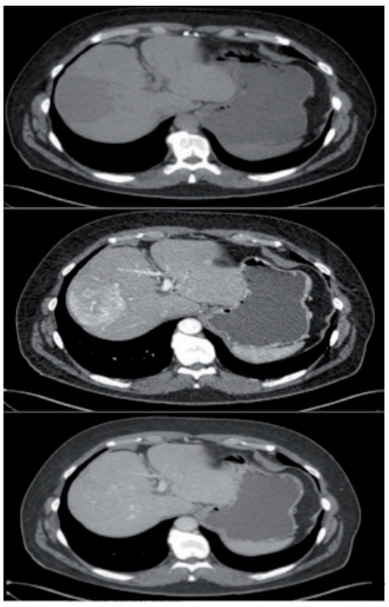


Case 3: CEOC Gastrointestinal 2016

53 yo engineer with abdominal cramps / diarrhea

- Exam: Appears well
- CBC, liver and renal function normal
- Poorly responsive to immodium
- Colonoscopy to cecum: negative
- CT:

CT scan: enhancing liver lesion



Non-contrast

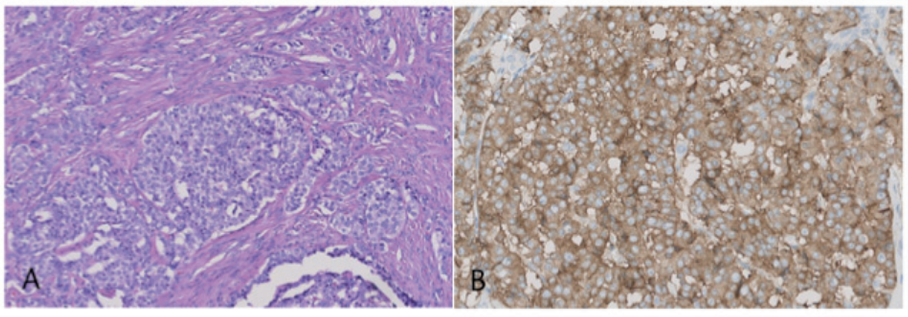
Arterial phase

Venous phase

AFP, CEA, CA19-9 normal
24 hr 5-HIAA normal
Chromogranin A 3 x ULN
CT: No primary identified

Liver biopsy

- Synaptophysin (+), chromogranin (+)
- Ki67 <1%, mitotic index: <2/10 HPF



H & E Synaptophysin

Koshimizu *et al*. Pancreas 41: 160-3, 2012.

CT C/A/P shows no primaryYou now offer:

A. Octreoscan (111In octreotide scan)

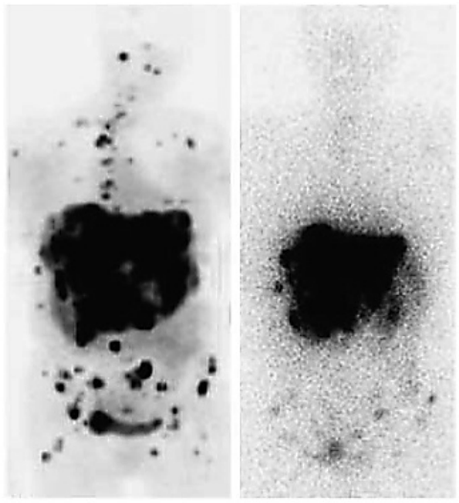
B. ^{68}Ga DOTATATE PET scan

C. Exploratory laparotomy

D. MRI cholangiogram

E. Endoscopic ultrasound

Functional imaging: PET

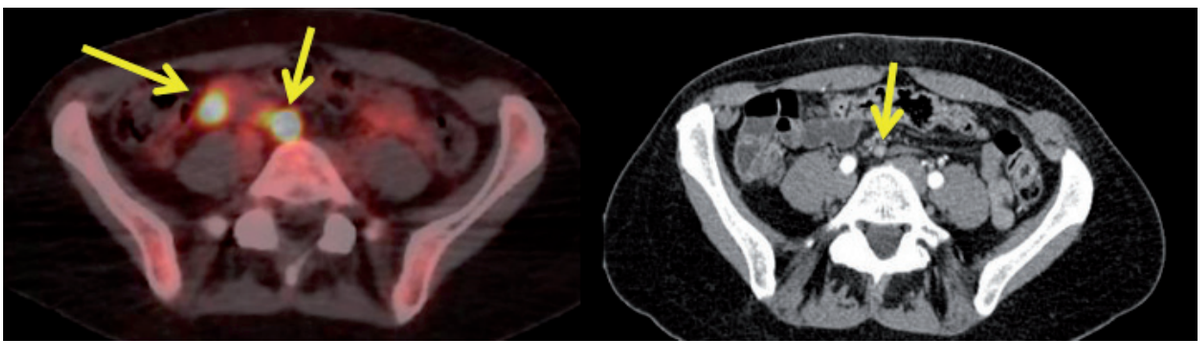


^{68}Ga-DOTATOC PET ^{111}In-DTPAOC SPECT

Increased sensitivity of ^{68}Ga-DOTATOC compared with ^{111}In-Octreoscan

Buchmann I et al: Eur J Nucl Med Mol Imaging 34:1617–1626, 2007

^{68}Gallium DOTATATE PET Scan



You now offer:

A. Resection of primary

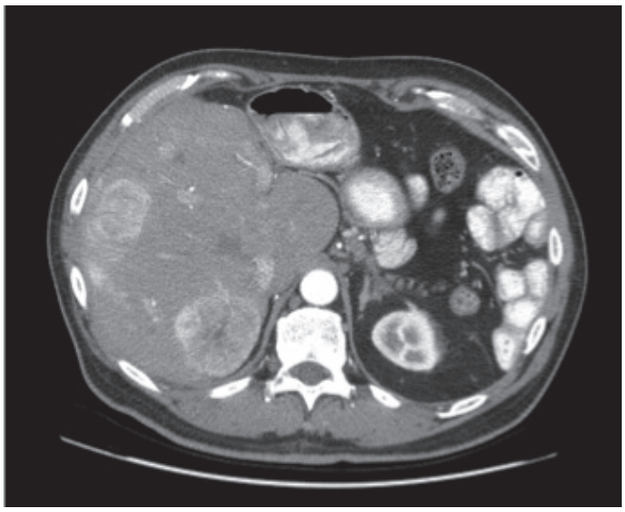
B. Somatostatin analogue (octreotide or lanreotide)

C. Everolimus

D. Peptide Receptor Radioligand Therapy (PRRT)

E. Sunitinib

Carcinoid symptoms resolve on lanreotide

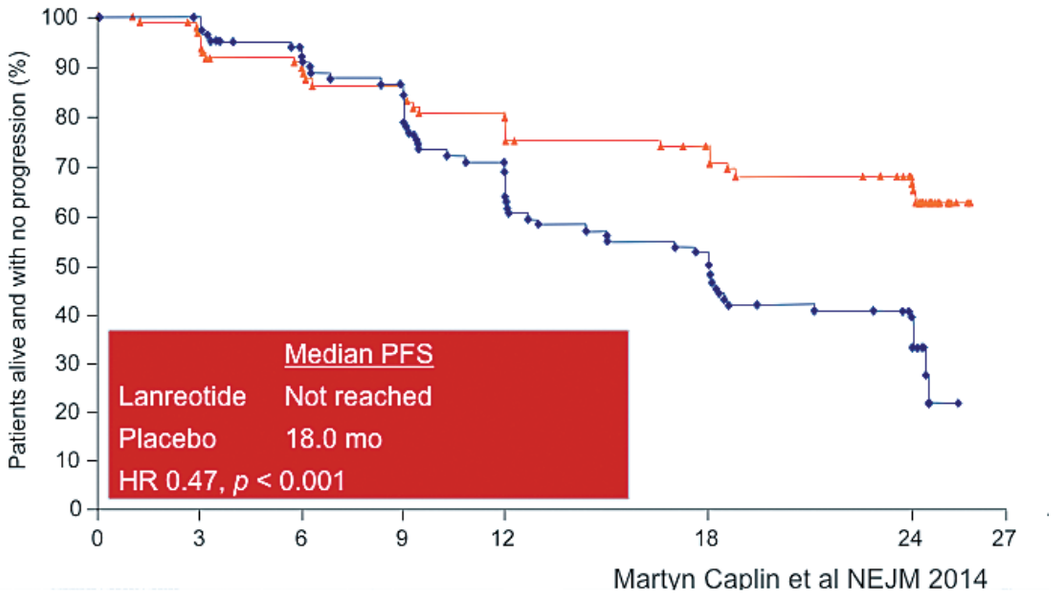


- But two years later, there is growth of liver lesions on scan
- LFTs are normal

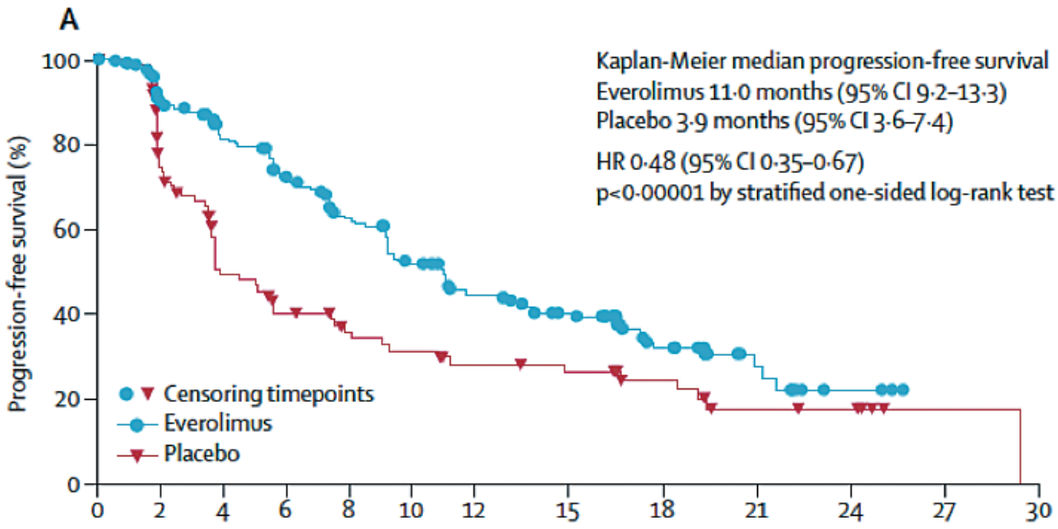
You now offer:

1. Everolimus
2. Peptide Receptor Radioligand Therapy (PRRT)
3. Interferon
4. Radioembolization with 90Y-spheres
5. Liver transplant

CLARINET TRIAL: Lanreotide vs placebo



Everolimus vs Placebo in non-pancreatic NET



James Yao et al. Lancet 2015

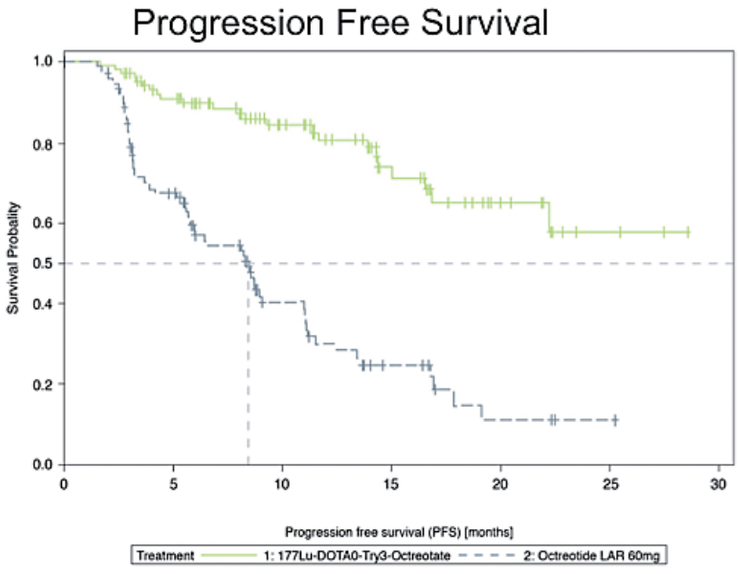
NETTER: Peptide Receptor RadiotherapyPRRT vs 2x dose octreotide in midgut NET

N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio : **0.21**
[0.129 – 0.338]
p < 0.0001

79% reduction in the risk of disease progression/death



Strosberg et al GI Cancer Symposium 2016

Take Home Points

- Many new options for managing neuroendocrine tumors and hormonal syndromes
- Seven (+) randomized trials in last 10 years
- Not everyone needs treatment: observation still valid option

Case 4: CEOC Gastrointestinal 2016

48 yo man with abdominal pain, weight loss

- Exam unremarkable, ECOG 1
- Labs: Hgb 10; MCV 68; Liver / renal function normal
- CT: multiple liver lesions and cecal mass
- Colonoscopy: cecal mass
- Path: poorly differentiated adeno; RAS / BRAF wild type

You now offer:

A. Resection of primary

B. FOLFIRI + EGFR inhibitor

C. CAPOX (or FOLFOX) + bevacizumab

D. FOLFOXIRI + bevacizumab

E. FOLFOXIRI

Which of the following is the least significant prognostic factor for metastatic colon cancer:

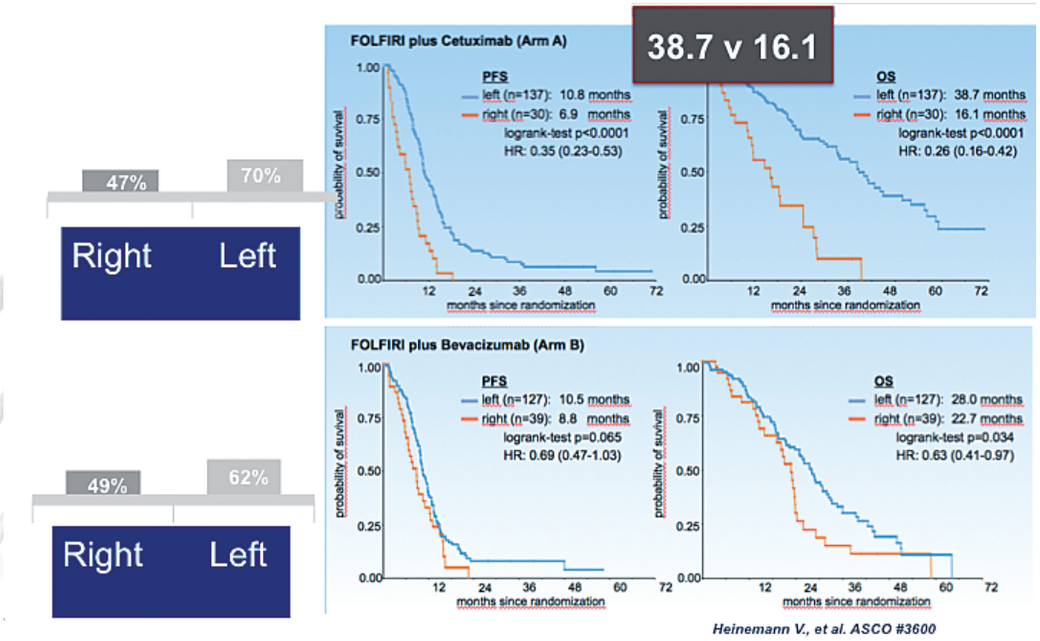
A. BRAF mutation status

B. Left versus right sided tumor

C. MSI status

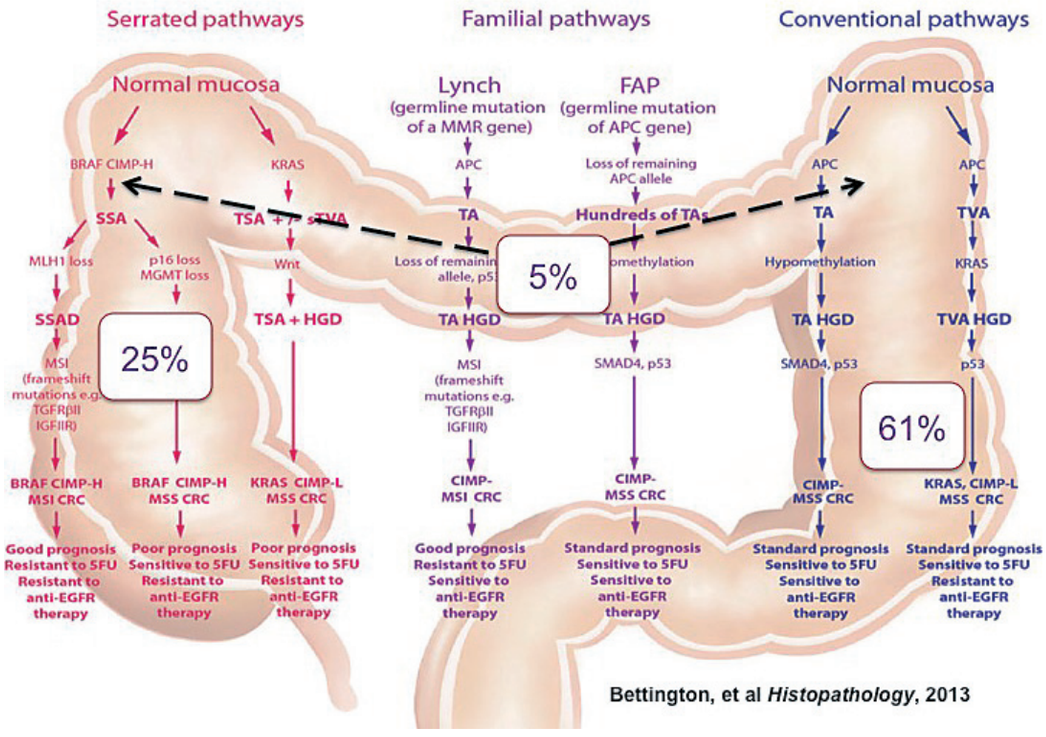
D. RAS mutation status

FIRE-3:Effect of Tumor localization on PFS and OS



Heinemann V., et al. ASCO #3600

Distribution of Primary Tumors in 80405



Bettington, et al *Histopathology*, 2013

80405: Outcomes by sidedness

	Right 1° OS (ms)	Left 1° OS (mos)	Hazard Ratio, 95% CI (R v L, adj)	Log Rank P Value (adj)
All KRAS wt N = 1137	19.4	34.2	1.56 (1.32,1.84)	P < 0.0001
	16.1 FIRE-3 **38.7**			
Cet	**22.7** FIRE-3 **28.0**		1.97 (1.56, 2.48)	
All				

Differences between FIRE-3 and 80405:

BEV patients have > OS in 80405 (by 2-4 mos)
Left-sided tumors: FIRE-3 = 77%; 80405 = 61%

Take Home Points

Side matters...

- Both prognostic and predictive?
- Should be stratification factor for future trials
- Should be routinely recorded in staging records
- Should EGFR inhibitors be used for right sided tumors??

Breast Cancers Tumor Board - 2016

SESSION CHAIR: Prof. Tanja Cufer, MD, PhD Medical Faculty Ljubljana, Slovenia

Faculty Panel

Medical Oncologists:

Alexandru Eniu (Romania),
Damir Vrbanec (Croatia),
Semir Bešlija (BiH)

Radiation Oncologists:

Lidija Beketić-Orešković (Croatia),
Jacek Jassem (Poland),
Eduard Vrdoljak (Croatia)

Surgical Oncologists:

Marko Snoj (Slovenia)

Case 1: CEOC Breast 2016

- A 47 year-old perimenopausal woman is being screened by mammography and suspicious lesion is found in the upper inner quadrant of the left breast.
- FNAB confirms breast carcinoma.
- Clinically and US negative axillary lymph nodes.
- Comorbidities : mild asthma
- Family history of breast and ovarian cancer: negative
- She undergoes left-sided modified radical mastectomy (MRM) with the following pathology:
    - **Infiltrating lobular carcinoma** of classical type and massive LCIS with multiple foci of ILC; the invasive component was pT2 (around 2, 5 cm) pN1 (1+ (4 mm) + 2 micro deposits/23 axillary nodes).
    - **Tumor biology**: G2 (Mitoses 1), Ki-67 up to 2%, ER 100%, PR 80%, HER2 negative (IHC 0, FISH 0.9).

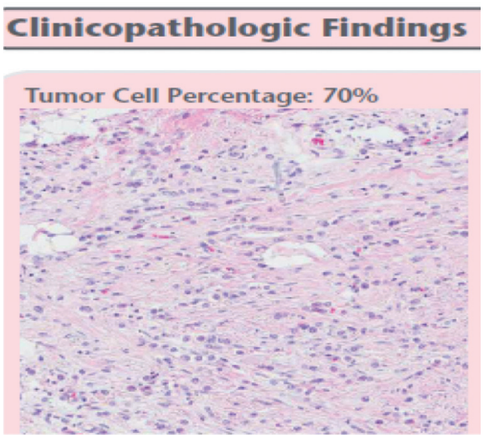
Question 1: Would you recommend adjuvant chemotherapy and if yes, which regimen would you choose?

1. Yes, anthracycline-based
2. Yes, anthracycline/taxane-based
3. No, only endocrine treatment
4. Order 1st-generation prognostic gene signature

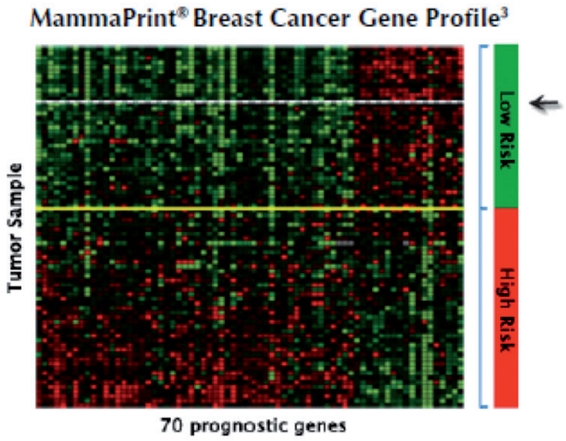
- The Oncotype DX® genomic profile showed RS 15 **? low risk group** with 10 % **probability of distant recurrence** within **10 yrs with TAM, with no benefit of adding Cht**.

Additionally, Mammaprint also showed a **low risk disease**.

Gene Profile Test Result



Low Risk



Due to nodal involvement the patient received 6 cycles of chemotherapy with anthracyclines (6X EC), without serious side effects

CIA developed after the 2nd cycle of CT.

CIA- chemotherapy-induced ammenorhea

Question 2: Which endocrine therapy would you recommend for the first 5 years?

1. Tamoxifen (TAM)
2. TAM 2-3 years, followed by AI, if becoming postmenopausal
3. OAS + AI
4. OAS + TAM

Question 3: Would you recommend irradiation?

1. No
2. Yes, chest wall
3. Yes, chest wall + axilla + SCL fossa
4. Yes, chest wall + radical node irradiation (RNI)

- The patient starts with TAM.
- She receives left-sided chest wall irradiation.
- After 2 years of TAM the tumor of the right ovary was found; **bilateral ovariectomy and histerectomy** revealed mature teratoma of the ovary.
    - She starts treatment with AI exemestane (and stays on it 5 years).
    - After 3 years of AI plus ovariectomy she starts with Zometa 4 mg i.v. /6 months due to osteopenia.

Question 4: What would you recommend now (after 2 years of TAM plus 5 years of AI)?

1. Stop ET
2. Continue with AI up to 10 years
3. Continue with TAM up to 10 years
4. Order second-generation gene signature to predict the risk of late relapse

- The patient starts with different AI (letrozole) because of some side effects of exemestane (steroidal effect) and continue with bisphosphonate zoledronic acid.
- Side effects of AI (LET) are manageable with mild arthralgias and hot flushes.
- After 2 yrs of TAM plus 8 yrs of AI she discontinues with ET.
- Dexa scan has improved with the bisphosphonate and calcium and vitamin D supplement. Lipid profile is normal.
    - 12 years after her primary diagnosis she has no evidence of disease.

Take Home Points

- Classical clinico-pathological and new molecular tools should be integrated and complementary in adjuvant Cht treatment decision-making for each individual patient.
- Recently presented results of the MINDACT trial (Piccart M, AACR 2016) showed a very high, 94.7% 5-year DMFS, in clinically high-risk/genomically low-risk (discordant) subgroup of patients; with no clinically meaningful differences in DMFS observed between the patients randomized or not to adjuvant Cht.
- For pre-/perimenopausal patients, tamoxifen remains the standard adjuvant ET, especially for those with low or/and intermediate-risk disease. Based on the results of the SOFT trial, the combination of AI plus OAS might be beneficial in younger patients with sufficient risk to warrant adjuvant ChT.
- The Overview meta-analysis confirmed a significant benefit of RT after mastectomy and axillary dissection in all patients with N+; with signif. 10-year gain in local recurrence of 16.7% and 20-year gain in breast cancer mortality of 7.9%, observed even in patients with 1-3 N+ and systemic therapy. No benefit was observed in the group of pts with No disease.
- After completion of 5 years of ET, the risk of relapse remains substantial in patients with HR-positive disease (approx. 5% annual risk of relapse with over 50% of all recurrences occurring after completion of 5 years of ET), with N-positive ILC patients being at particular high risk of late relapses.
- Extended endocrine therapy from 5 to 10 years reduces the risk of late relapses and breast cancer mortality during the second decade after diagnosis by approx. one third. However, the potential toxicity must be taken into consideration in each individual patient.
- In patients being premenopausal at the time of diagnosis and becoming postmenopausal during the first 5 years of tamoxifen a switch to AI, seems to be particularly beneficial (MA.17 trial HR 0.25).
- In premenopausal patients extended therapy with TAM up to 10 years significantlly improves RFS and BCSS (ATLAS and longer follow-up aTTom trial data).
- The benefit of extended HT of more than 10 years is being evaluted in the MA.17R trial, the results are eagerly awaited.

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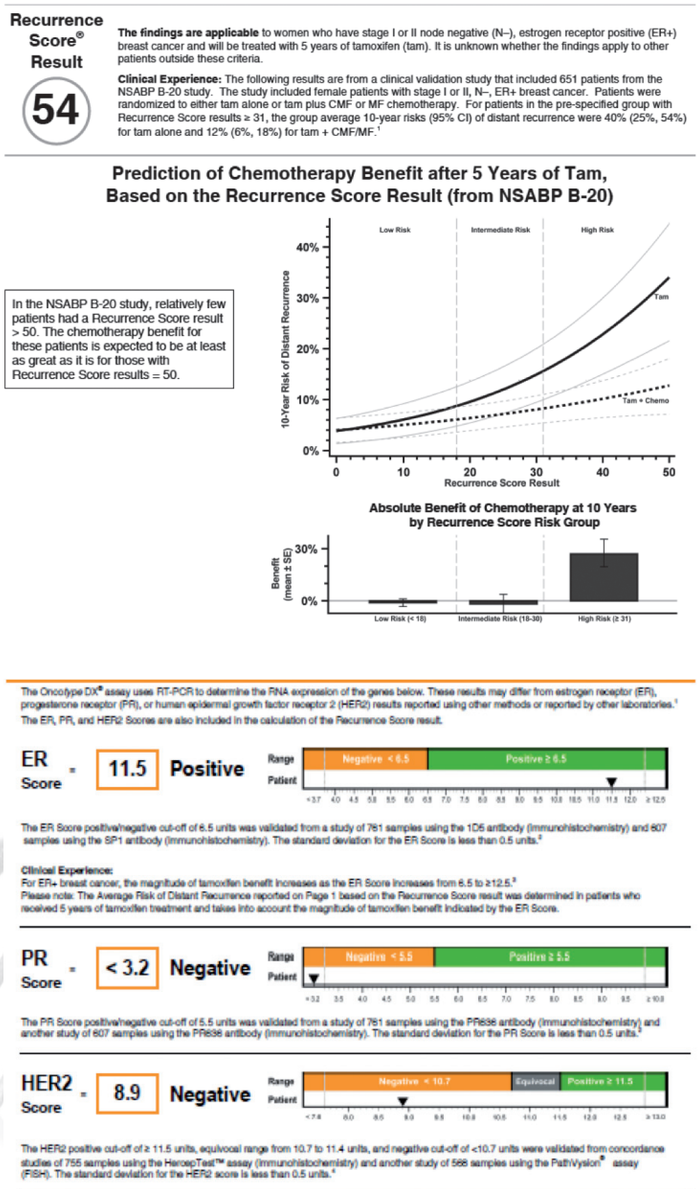
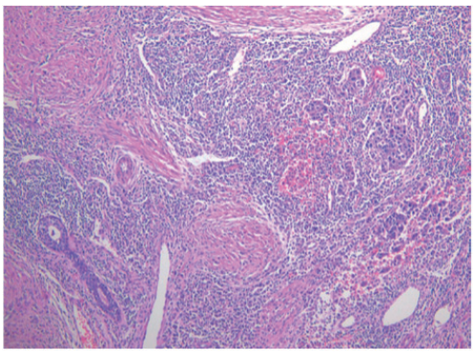
Case 2: CEOC Breast 2016

- A 60 year-old postmenopausal woman, without comorbidities, is found to have a 3 cm tumor in her right breast by physical examination.
- FNAB confirms breast carcinoma.
- Clinically and according to US neg. axillary lymph nodes.
- Family history of ovarian cancer (the mother diagnosed with OC at age 70)
    - She undergoes right-sided mastectomy with SLNB with the following pathology:
    - **Invasive ductal carcinoma** of no special type, pT2 (2.8 cm) pN0 (0/4).
    - **Tumor biology**: G3 (Mitoses 3), Ki-67 at least 50%, ER 100%, PR 5%, HER2 negative (IHC 2+, FISH 1.1).





Question 1: What regimen would you recommend for adjuvant CT?

1. Sequential standard anthracycline-taxane-based regimen
2. Concomitant anthracycline-taxane-based regimen (e.g. TAC)
3. Platinum-based regimen (according to positive familiar history for OC)
4. Sequential dose-dense anthracycline-taxane-based regimen

- She receives adjuvant chemotherapy with the dose-dense scheme (ACx4, paclitaxel was given weekly -8x). Primary prophylaxis with pegfilgrastim is initiated.
    - Severe leucocytosis after pegfilgrastim injections is documented and after the 3rd cycle of paclitaxel she developes Grade 2 sensoric neuropathy.

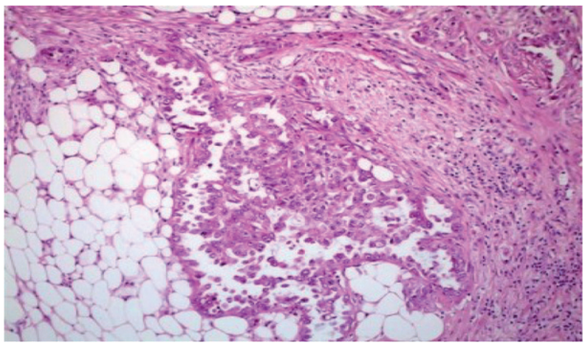
Question 2: What ET would you propose for this patient and would you recommend a bone modifying agent (BMA)?

1. AI for 5 yrs, zoledronic acid every 6 months
2. AI for 5 yrs followed by TAM for 5 yrs, zoledronic acid every 6 months
3. AI for 10 yrs, denosumab (60 mg) or zoledronic acid every 6 months
4. AI for 5 yrs, no BMA, just regular bone density evaluation

- She starts with AI anastrozole and zoledronic acid 4 mg i.v. per 6 months.
- The patient reports of moderate osteomuscular pain in big and small joints, neuropathy is slowly improving to Grade 1.
- In September 2015 (5 months after the end of adjuvant CT for breast cancer) she is found to be a BRCA 1 mutation carrier (the testing was done based on family history of OC).

Question 3: What would you consider the best risk reduction strategy for this patient ?

1. Contralateral mastectomy
2. Risk-reducing salphingo oophorectomy (RRSO)
3. Both, 1 and 2
4. Nothing



- November 2015: during RRSO the tumor of the left Fallopian tube is found, suspected for primary Fallopian tube cancer.
- She undergoes laparotomy with omentectomy, histerectomy, bilateral oophorectomy and left pelvic lymphadenectomy. The histology reveals a **high grade serous adenocarcinoma of the left Fallopian tube (4 cm), FIGO stage III A, R0 resection**, ER 90%, PR 0%.
- MDTB suggests adjuvant chemotherapy (Residual neurotoxicity G1 after adj CT for breast cancer).

Question 4: What regimen of adjuvant CT for ovarian cancer would you propose?

1. 6 cycles with paclitaxel and carboplatin
2. 6 cycles with liposomal doxorubicin and carboplatin
3. 6 cycles of carboplatin monotherapy
4. 4 cycles with docetaxel and carboplatin

- She has recently finished with adjuvant CT for Fallopian tube cancer with paclitaxel and carboplatin. She was tolerating the chemo regimen well, with no major side effects and no worsening of neuropathy.
- After discontinuation of CT, she continues with anastrozole.

Take Home Points

- A systematic review and meta-analysis of the trials evaluating the role of DD CT showed significant improvement in disease-free (HR= 0.81) and overall survival (HR= 0.85) for the latter. The benefit has been observed for ER-negative and for high risk disease (high Ki-67 index, etc.). There was no increase in overall treatment-related AEs associated with DD approach.
- The majority of clinically ER+ breast cancers being classified as high-risk according to the Oncotype Dx RS and/or Mammaprint profile represents a luminal-B-like intrinsic subtype of the disease. The latter is genomically much more altered than luminal –A-like one and is more similar to basal-like.
- Luminal B cancers have much worse outcomes compared to luminal A, the outcomes of luminal B being comparable to, if not worse than that of the basal-like and HER2-enriched subtypes, especially on long-term.
- No statistically significant differences in OS, DFS, and toxic effects between concurrent and sequential adjuvant chemo- and endocrine therapy for early breast cancer (EBC) have been observed so far.

- The average risk for breast cancer in BRCA1 mutation carriers by the age of 70 years is 65% and for ovarian cancer 39%. The contralateral breast cancer risk in BRCA1 carriers is 27% within 5 years of the initial breast cancer diagnosis.
- In BRCA1/2 mutation carriers RRSO reduces the risk for ovarian/fallopian and for breast cancer by approx. 80% and 50%, respectively; leading to a reduction of breast cancer and ovarian cancer – specific mortality (HR 0.44 and HR 0.21, respectively. Risk-reduction mastectomy reduces the risk for breast cancer by approx. 93% .
- Standard CT for ovarian/fallopian cancer consists of a combination of paclitaxel and carboplatin, every 3 weeks. For those patients who develop an allergy to or do not tolerate paclitaxel, the combination of docetaxel-carboplatin or pegylated liposomal doxorubicin (PLD)-carboplatin can be considered, based on two randomized clinical trials showing similar efficacy.

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Case 3: CEOC Breast 2016

- A 35 year-old premenopausal woman on self exam observes a 2.5 cm lump in the left upper outer quadrant
- No pregnancies
- Mammography reveals a 2.3 cm spiculated mass in her left upper outer breast
- FNAB confirms breast carcinoma.
- Clinically and US negative axillary lymph nodes.
- She undergoes left-sided lumpectomy and SLNB with the following pathology:
    - **Infiltrating ductal carcinoma** pT2 (around 2, 2 cm) with micropapillary features, pN1 (1/3) R0.
    - **Tumor biology**: G2 (Mitoses 1), Ki-67 40%, ER 0%, PR 0%, HER2 negative (IHC 0).

Question 1: What local therapy would you recommend further?

1. Left axillary node dissection
2. Whole breast irradiation
3. Whole breast irradiation + axilla irradiation
4. Whole breast irradiation + radical node irradiation (RNI)

Question 2: Which drug would you recommend to add to anthracycline-taxane adjuvant CT?

1. Capecitabine
2. Gemcitabine
3. Bevacizumab
4. Platinum
5. None

Question 3: What type of fertility preservation technique would you consider?

1. Ovarian function suppression with LHRH agonists
2. Oocytes cryopreservation
3. Embryo cryopreservation
4. None

- She receives CT with anthracycline (4X EC) and taxane (paclitaxel weekly for 12 weeks) with LHRH agonist and WBI.
- After 2 years of follow-up, patient presents with persistent cough.
- CT exam evaluation reveals progressive disease: multiple micronodules disseminated in the lungs, max diameter 1.2 cm.

Question 4: What would you recommend at this point?

1. Biopsy of one of the lung nodules
2. Platinum based-chemotherapy
3. Consider including patient in clinical trial of PARP inhibitor (olaparib)
4. Consider including patients in clinical trials with immunotherapy (pembrolizumab)

- The patient receives Docetaxel+ Carboplatin without response (CT scan lung nodules progression after 2 cycles).
- Now, she is under screening for inclusion in a clinical trial with immunotherapy.

Take Home Points

- Avoiding axillary dissection for patients with one or two metastatic lymph nodes proved safe in a large institutional series, confirming the applicability of randomized trial approaches (ACOSOG Z011, AMAROS) for the majority of women with T1 and T2 clinically node negative breast cancer.
- Two recent radiotherapy trials in node positive disease found superior disease control with extended radiation fields which included regional lymph node areas.
- In triple negative disease, adjuvant chemotherapy should include an anthracycline and taxane, no other chemotherapy agent proved added efficacy.
- Immune checkpoint inhibition (CPI) has been demonstrated to be an effective anticancer strategy. Several lines of evidence support the study of immunotherapy in triple-negative breast cancer (TNBC). Several CPIs are currently under investigation in TNBC.

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Case 4: CEOC Breast 2016

- A 60 year-old postmenopausal woman, is found to have a 5.5 cm tumor in her right breast.
- No comorbidities
- Clinically and according to US positive axillary lymph nodes.
- Family history of breast or ovarian cancer –negative.
- True-cut biopsy:
    - **Invasive ductal carcinoma** of no special type.
    - **Tumor biology:** G3 (Mitoses 3), Ki-67 at least 90%, ER 15%, PR 5%, HER2 positive (IHC 3+).

Question 1: What regimen do you recommend for neoadjuvant CT?

1. Anthracylines followed by taxane plus trastuzumab
2. TCH (docetaxel, carboplatin + trastuzumab)
3. Taxane plus trastuzumab plus pertuzumab followed by adjuvant FEC
4. Anthracycline-taxane with concomitant trastuzumab

- Patient receives neoadjuvant chemotherapy 4xEC→ 12 X paclitaxel weekly plus trastuzumab.
- She developes Grade 2 sensoric neuropathy,.
    - She undergoes right-sided mastectomy with ALND with the following pathology:
    - **Invasive ductal carcinoma**, pT1c (1.1 cm) pN1 (3/15).
    - **Tumor biology**: G3 (Mitoses 3), ER 5%, PR 0%, HER2 positive (IHC 3+).

Question 2: What HER2-directed therapy would you recommend after surgery?

1. Trastuzumab for six months
2. Trastuzumab for one year
3. Trastuzumab plus lapatinib for one year
4. Trastuzumab and pertuzumab for one year

- The patient receives Trastuzumab iv every 3 weeks. Cardiac evaluation is performed every 3 months, after 6 months of treatment LVEF drops from 60% to 48%.
  No clinical signs of cardiac failure.

Question 3: What do you recommend?

1. Stop trastuzumab permanently
2. Discontinue trastuzumab for one month and repeat LVEF
3. Continue trastuzumab
4. Switch to lapatinib

- After 1 months off trastuzumab her LVEF returnes to normal value (55%). She completes 1 year of trastuzumab.
- She is currently receiving AI plus BMA with no sign of disease for four years.

Take Home Points

- AnthracyPertuzumab was the first drug granted accelerated FDA approval for the neoadjuvant treatment of HER2-positive breast cancer using a pCR endpoint.
- In patients who can tolerate it, use of anthracycline-taxane Cht regimen is considered optimal, while in patients with a higher risk of cardiotoxicity DCarbo regimen might be used.
- Trastuzumab should be preferentially administered concurrently with a non-anthracycline, but not with anthracycline Cht.
- There is no data to support dual HER2 blockade in the adjuvant setting, 1 year of trastuzumab is a standard care.
- Patients receiving adjuvant HER2-directed therapy require regular cardiac function monitoring (LVEF measurement). If cardiac toxicity occurs it is usually reversible.

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Alex Eniu, MD, Nicoleta Antone, MD

Scientific Program:

Abstracts

3D-IMAGE GUIDED BRACHYTHERAPY IN THE TREATMENT OF PATIENTS WITH NASOPHYARYNGEAL CANCER

1

Marin Prpic[1], Jure Murgic[1], Marin Gregov[1], Blanka Jaksic[1], Mirjana Budanec[1], Iva Mrcela[1], Mihaela Mlinaric[1], Ante Bolanca[1], Zvonko Kusic[1], Ana Frobe[1]

[1] Department of oncology and nuclear medicine, University Hospital Center, Zagreb, Croatia

Introduction: 3D image guided high-dose-rate brachytherapy (HDR-BT) is therapeutic option in the treatment of patients with nasopharyngeal carcinoma (NPC). Herein we report technique and early results of HDR-BT used for patients with NPC referred to our Institution.

Patients & Methods: Between 2013 and 2015, a total of 7 patients received intracavitary HDR-BT for NPC. Patients were immobilized in the supine position. Nasopharyngeal brachytherapy applicator (plastic hollow tube that follows nasopharyngeal curvature) was placed at treatment position. Radio-opaque dummy wire was placed into applicator lumen for purpose of aplicator imaging and verifying relation of applicator with tumor and organs-at-risk. Simulation CT was obtained with 1-3 mm slice thickness with applicator in situ and 3D treatment planning system (Brachyvision, Varian) was used. The GTV was determined as the macroscopic extent of the persistent disease previously defined on MRI. The high- risk CTV included the persistent disease plus 0.5 cm margin around the GTV. Brachy-therapy dose was prescribed on CTV with aim of maximal covering of the CTV while respecting organs-at-risk dose constraints. The treatment was delivered using HDR afterloader (GammamediX+, Varian) with Ir-192 source.

Results: All patients completed planned brachytherapy treatment: to a dose of 9 Gy in 3 fractions (one fraction weekly) for adjuvant boost to EBRT in 2 patients, and to median dose of 15 Gy range, 9-24 Gy) in 3-8 fractions (one fraction weekly) for salvage treatment after failure of previous EBRT. Median time from EBRT to HDR-BT was 15 months (range, 1-64 months) and median dose of the previous EBRT was 70 Gy (range, 66-74 Gy). After median of follow-up of 9 months from start of HDR-BT (range, 8-25 months), no patient in adjuvant setting experienced failure. Three patients with recurent or persistent disease after EBRT experienced local failure, with median time to local progression of 8 months and they died as a result of regionally progressive disease. Remaining two patients with recurrent or re-sidual disease experienced complete response to HDR-BT and remained disease-free.

Conclusion: Described technique allows safe treatment of NPC, specially in adjuvant setting. Efficacy of salvage HDR-BT for recurrent or residual NPC heavily depends on extent of disease, with well con-troled recurrences within the nasopharynx.

ADHERENCE TO AROMATASE INHIBITORS, VITAMIN D AND CALCIUM IN BREAST CANCER PATIENTS IN CROATIA

2

Eduard Vrdoljak[1], Lidija Boskovic[1], Maja Gasparic[2], Ingrid Belac Lovasic[3], Zeljko Soldic[4], Branka Petric Mise[1], Marijana Jazvic[4], Ljubica Vazdar[4], Liliana Bozac Radolovic[5], Josipa Jovic Zlatovic[6], Marija Petkovic[3], Damir Gugic[7]

[1] Clinic for Oncology and Radiotherapy, University Hospital Center Split, Split, Croatia

[2] Medical Affairs, PLIVA Croatia LTD, Zagreb, Croatia

[3] Clinic for Oncology and Radiotherapy, University Hospital Center Rijeka, Rijeka, Croatia

[4] Department of Oncology and Nuclear medicine, University Hospital Center Sestre Milosrdnice, Zagreb, Croatia

[5] Department of Oncology, General Hospital Pula, Pula, Croatia

[6] Department of Oncology, General Hospital Šibenik, Šibenik, Croatia

[7] Clinic for Oncology and Radiotherapy , University Hospital Osijek, Osijek, Croatia

Background: Lack of adherence of breast cancer patients to adjuvant hormonal therapy was reported in different retrospective and prospective studies in Western countries. We initiated prospective non-interventional study to investigate adherence to non-steroidal aromatase inhibitors, vitamin D and calcium in postmenopausal patients with early hormone positive breast cancer receiving adjuvant therapy in Croatia.

Material and methods: Patients with hormone dependent breast cancer receiving non-steroidal aromatase inhibitors (anastrozole or letrozole) in adjuvant setting were enrolled in this prospective non-interventional study. Both newly diagnosed patients and those already receiving non-steroidal aromatase inhibitors for up to 3.5 years were included. Self-reported adherence was the primary endpoint of the study. Patients were asked to fill in diaries and to report number of doses that were omitted on monthly basis. Patients who took more than 80% of doses were considered adherent.

Results: A total of 438 patients were included in the study and were followed up for an average 23.5 ±4.9 months. Adherence to non-steroidal aromatase inhibitors was reported in 97.0% of patients. A total of 329 (75.1%) patients received vitamin D and/or calcium at least at some time point during this study and provided information on the adherence. Lower adherence to the vitamin D and calcium than to aromatase inhibitors was observed; 88.4% of patients were adherent based on their reports. Forgetting to take medication was reported as the most common reason for omitting doses for both, aromatase inhibitors and vitamin D/calcium. Lack of physicians' adherence to guidelines on bone health in breast cancer patients treated with aromatase inhibitors was observed. A total of 324 (74.0%) patients received vitamin D and 317 (72.4%) patients received calcium either as mono preparation or as fixed combination supplements.

Conclusion: Self-reported adherence to aromatase inhibitors in breast cancer patients in Croatia was similar to those reported in other studies. The adherence to vitamin D and/or calcium was lower than the adherence to aromatase inhibitors. Additionally, there is lack of physician's adherence to guidelines on bone health in patients treated with aromatase inhibitors.

ADHERENCE TO AC DOSE DENSE CHEMOTHERAPY PROTOCOL RHYTHM IN EARLY AND LOCALLY ADVANCED BREAST CANCER PATIENTS

3

Sanja Maloševac1, Ana Tečić-Vuger2, Mirjana Pavlović2, Davor August3, Andrea Jurić2

[1] Department of Internal medicine, Nephrology and Haematology, General Hospital, Sisak, Croatia

[2] Department of Medical Oncology, University of Zagreb, University Hospital Center »Sestre milosrdnice«, University Hospital for Tumors, Zagreb, Croatia

[3] Department of Internal medicine, Medical Oncology and Haematology, General Hospital, Karlovac, Croatia

Breast cancer as the most common cancer in women is an area of intensive search for the most efficient and simultaneously satisfying and tolerable treatment. This is review of our experience in treating early and locally advanced breast cancer patients with dose dense regimen of anthracycline chemotherapy protocol (adriamycin + cyclophosphamide) and adherence to chemotherapy rhythm. We conducted a retrospective study on 53 female patients treated with dose dense AC x4 followed by weekly paclitaxel x12 +/- trastuzumab x17 every 3 weeks for breast cancer at the Department of medical Oncology, University Hospital for Tumors, University Hospital Center „Sestre milosrdnice“ from April 2014 to April 2016. Data were collected from medical records. Patients were aged 30-64 years (median 44 years). Patients were treated in adjuvant or neoadjuvant setting. One patient has been lost to follow-up. In one patient, after 2 cycles of dose dense AC (DD AC) in two week cycles, because of fever, leukocytosis and fatigue, therapy has been continued in three week cycles. In 1 patient after 3 cycles DD AC, therapy was stopped due to the signs of cardiotoxicity. In the remaining 50 patients 4 cycles of DD AC were administered, out of which in total only 4 cycles have been delayed in 3 patients. This means the delay of 0.66 day per patient or 0,165 days per cycle. Delays were due to respiratory infection and neutropenia (in one patient therapy continued with 20% reduction in the dose). Therapy was continued with weekly paclitaxel or weekly paclitaxel + trastuzumab every 3 weeks. Our analysis showed that there was high level of maintenance of chemotherapy rhythm achieved in breast cancer patients treated with DD AC therapy.

CHARACTERISTICS OF THE PATIENTS WITH LUNG CANCER WITH OR WITHOUT COPD

4

Ivona Markelić[1], Lela Bitar[1], Fran Seiwerth[1], Miroslav Samaržija[1], Marko Jakopović[1]

[1] Department of respiratory disease, University hospital centre Zagreb, Zagreb, Croatia

Introduction: Lung cancer (LC) and chronic obstructive pulmonary disease (COPD) are leading causes of morbidity and mortality worldwide. We have compared mOS (median overall survival) in patients suffering from both lung cancer and COPD in to that suffering from lung cancer alone. We have also analyzed demographic characteristics and differences among patients with LC and with or without COPD.

Materials and Methods: Total of 1359 medical records of patients diagnosed with lung cancer Clinical hospital center Zagreb, Department of respiratory diseases Jordanovac during the year 2012 and 2013 were retrospectively collected and reviewed. mOS was measured and analyzed using the Kaplan-Meier and log-rank test.

Results: 386 of 1359 patients (28%) were diagnosed with LC and COPD (12 were missing). From those 386 patients, 80.6% were male with stage IV (44%), median age 66.01 years. 64.8 % had very good performance status (ECOG 0), 54% were ex smokers while 39.5% were current smokers with the median of 56.28 pack years. 39.6% were diagnosed with squmaous cell LC, 34.25% with adenocarcinoma, 13.0 % with small cell LC (SCLC). 74.4 % had no emergency presentation and those who had were presented with haemoptysis (38.8%). 11.4% of them underwent surgical treatment, 22% had radiotherapy. They were mainly treated with chemotherapy, 74.6% received 1 line chemotherapy.

961 patients diagnosed with LC had no COPD. 65.9% were male with stage IV, median age 63.3 years. 69.6% had very good performance status (ECOG 0). 48% were ex smokers, 38.5% were current smokers with the median of 44.69 pack years. 50.6 % were diagnosed with adenocarcinoma, 22.3% with squamous cell LC, 13.3% with SCLC. 80.1 % had no emergency presentation, and those who had have presented with the haemoptysis (26.3%). 12.1% underwent surgical treatment, 23.1% had radiotherapy. 79.8% received 1line chemotherapy.

mOS of the patients with lung cancer was 9 months, regardless of the COPD. Also no significant difference in survival between different histological types of lung cancer was observed between those patients.

Conclusion: The prognostic impact of COPD on lung cancer is unclear, further investigations are necessary to define links between COPD and LC. The underlying mechanism by which COPD affects the prognosis of LC remains elusive.

CLASSIFICATION OF PATIENTS WITH HER2+ BREAST CANCER TREATED BY TRASTUZUMAB ACCORDING TO RISK OF ILLNESS PROGRESSION; CROATIAN NESTED CROSS-SECTIONAL STUDY

5

Davor August[1], Ana Tečić Vuger[2], Mirjana Pavlović[2], Tajana Silovski[2], Žarko Bajić[3]

[1] *Department for Internal Medicine, Medical Oncology, Hematology and Nephrology, General Hospital Karlovac, Karlovac, Croatia*

[2] *Department of Medical Oncology, University Hospital for Tumors, Clinical Hospital Center "Sestre milosrdnice", Zagreb, Croatia*

[3] *Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia*

Addition of trastuzumab to adjuvant chemotherapy regimens provides substantial benefit for women with HER2-positive breast cancer, both in terms of disease recurrence and survival. Objective of our study was to classify patients with HER2+ breast cancer treated with trastuzumab according to risk of disease progression, based on their demographic, vital and clinical characteristics at the time of diagnosis. This one-center, post-marketing, open label, nested cross-sectional study enrolled patients from June 2012 to March 2015. Enrollment was ended on March 13th 2015. The study was conducted at the Department of Medical Oncology of University Hospital for Tumors in Zagreb, Croatia. Targeted population was the general population of patients with HER2 positive breast cancer, ECOG status 0 or 1, adjuvantly treated with trastuzumab. We included the consecutive sample of all patients initiated to trastuzumab during the enrollment period. Total of 225 patients were included. Their median age was 60 (52-67) years. Their median body mass index was 26 (23-30) kg/m2. Tumors were estrogen positive in 61.8% and progesterone positive in 49.3% of patients. At the time of diagnosis 12.7% of patients had metastatic disease. Disease progression was experienced by 17.9% of patients. Overall CART classification tree with Thoing criterion predictive accuracy for disease progression was statistically significant (p=0.026). Proportion of cases correctly classified as having a progression was 82%. Classification resulted in four final groups of patients. Two groups with risk of progression higher than the average, and two with risk below the average. Two final groups with high risk of progression were: 1) patients with metastatic disease and 2) patients without metastases, with negative estrogen receptors, and body mass index > 28.4 kg/m2. Two final groups with lower risk of progression were: 1) patients without metastases, with negative estrogen receptors, but, in contrast to previous group, with body mass index ≤ 28.4 kg/m2 and 2) patients without metastases with positive estrogen receptors. In conclusion, according to our data, overweight early breast cancer patients whose tumors do not express estrogen receptors have the highest risk of disease progression.

COMPLETENESS OF DATA ON MALIGNANT MELANOMA SKIN-SITE AND MORPHOLOGY IN CROATIAN NATIONAL CANCER REGISTRY 2000-2014: AN OVERVIEW OF RECENT PROGRESS.

6

Jelena Barbaric[1], Jan Willem Coebergh[2], Mario Sekerija[3]

[1] *Andrija Štampar School of Public Health, School of Medicine, University of Zagreb, Zagreb, Croatia*

[2] *Department of Public Health, Erasmus University Medical Center, Rotterdam, Netherlands*

[3] *Croatian National Cancer Registry, Croatian Institute of Public Health, Zagreb, Croatia*

Malignant melanoma of the skin (MM) mortality rates and five-year relative survival in Croatia are poor compared to most European countries. Epidemiological data recorded at the National Cancer Registry (CNCR) are used for informing various decision-makers and researchers, as well as comparisons with other countries. We analysed CNCR data on MM skin-sites and morphology for the 2000-2007 and 2008-2014 periods and compared them with European 2000-2007 data. We further stratified skin-site analyses in Croatia by sex, different age groups, and sources of reports. We found 52% of 'non specified sites' cases in Croatia in 2000-2007, however that proportion decreased to 36% in 2008-2014, with 29% of registered MM cases occurring on trunk, 22% on limbs, and 13% on head and neck. The proportion of 'non specified sites' cases in reports originating from university hospitals decreased by 25% and in those from general hospitals by 9.2%. The proportion of 'not otherwise specified' among histologically verified cases decreased from 96% in 2000-2007 to 84% in 2008-2014. Our results reveal a substantial proportion of inadequately reported cases, in particular when compared to data at European level where in 2000-2007 only 7.7% of cases were from 'non specified sites' and 19% were of non-specified morphology. Irrespective of recent progress, the proportion of unspecified cases still hampers insight into site-distribution by subgroups. Further increase in overall completeness of MM data within CNCR is needed to enable research-informed improvement of melanoma control in the country. Our findings call for engagement of all stakeholders in optimisation of the national melanoma registration processes, and using models such as RegisTree.

CONCORDANCE BETWEEN CLINICOPATHOLOGIC PARAMETERS AND GENOMIC PROFILES IN EARLY-STAGE BREAST CANCER PATIENTS: SLOVENIAN EXPERIENCE

7

DOMEN RIBNIKAR[1], Tanja Čufer[2], Aleksander Sadikov[3]

[1] Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia

[2] Medical Oncology, University Clinic Golnik, Golnik, Slovenia

[3] Faculty of Computer and Information Science, University of Ljubljana, Ljubljana, Slovenia

Introduction: The advent of genomic signatures in early-stage breast cancer (EBC) allowed us to better understand its biology and led to more individualized systemic treatment approaches. First-generation gene signatures such as the Oncotype Dx RS may help us better tailor adjuvant systemic chemotherapy (CT) in HR+ EBC however currently they are not used in everyday clinical practice.

This retrospective double-institution clinical cohort series aimed to determine how one of first-generation gene expression profiles (Oncotype Dx RS) correlates with specific clinicopathologic parameters, namely lymph node status, PR expression and Ki-67 levels in a real - life setting.

Patients and methods: 20 patients with EBC that had Oncotype Dx RS done on their primary tumors were identified through our pathology computer database retrospectively. The clinical information and follow-up were obtained from the patients' electronic medical record.

Data collected included all pathology breast tumor parameters (tumor size, histologic type and grade, lymph node status, ER, PR and HER-2 expression and Ki-67 levels (cut off > 15%)).

Concordance between lymph node status, PR expression and Ki-67 score with RS gene expression was planned to be calculated but according to a small number of patients it would be statistically not meaningful. The average and median clinical follow-up time for all of the cases included in the study were 34.2 months, ranging from 1 month to 146 months.

Results: Of the total 20 patients, no cases were found to have T3 or T4 tumors while 12 cases (12/20; 60%) presented with lymph node metastases; 1 patient had even 4 positive lymph nodes. All patients were highly ER positive and HER2 negative. Other patients' characteristics are presented in Table 1.

Oncotype Dx RS stratified 60% of patients into the low-risk group (12/20), 25% into the intermediate-risk group (5/20), and 15% into the high-risk group (3/20).

The morphologic and IHC characteristics of each tumor were then examined with respect to stratification by the RS score (Table 1).

Table 1: Data summary of all patients

	Low risk RS	Intermediate risk RS	High risk RS
Tumor size (average)	2.41 cm	1.98 cm	2.66 cm
T 1	4/12 (33.3%)	4/5 (80%)	0/3 (0%)
T2	4/12 (33.3%)	1/5 (20%)	3/3 (100%)
Histological type	IDC 10/12 (83.3%), ILC 1/12 (8.3%), MUC 1/12 (8.3%)	IDC 2/5 (40%), ILC 3/5 (60%)	IDC 2/3 (66.6%), ILC 1/3 (33.3%)
Grade I	2/12 (16.6%)	0/5 (0%)	0/3 (0%)
Grade II	9/12 (75%)	5/5 (100%)	2/3 (66.6%)
Grade III	1/12 (8.3%)	0/5 (0%)	1/3 (33.3%)
Positive lymph nodes	9/12 (75%)	2/5 (40%)	1/3 (33.3%)
ER +	12/12 (100%)	5/5 (100%)	3/3 (100%)
ER -	0/12 (0%)	0/5 (0%)	0/3 (0%)
PR +	12/12 (100%)	4/5 (80%)	1/3 (33.3%)
PR -	0/12 (0%)	1/5 (20%)	2/3 (66.6%)
HER-2 +	0/12 (0%)	0/5 (0%)	0/3 (0%)
HER-2 -	12/12 (100%)	5/5 (100%)	3/3 (100%)
Ki-67 +	1/12 (8.3%)	1/5 (20%)	1/3 (33.3%)
Ki-67 -	11/12 (91.6%)	4/5 (80%)	2/3 (66.6%)

We found that of the HR, IR and LR stratified patients, 3/3 (100 %), 1/5 (20 %) and 3/12 (25 %) received adjuvant CT, respectively (Table 2). All patients received adjuvant endocrine therapy. No recurrences have occurred in any of the patients studied so far.

Table 2: Data showing RS results and actual recurrence/metastasis and whether patients received CT or not

	Low risk RS	Intermediate risk RS	High risk RS
Number (%)	12 (60%)	5 (25%)	3 (15%)
Patients with recurrence/metastasis	0 (0%)	0 (0%)	0 (0%)
Chemotherapy received	3/12 (25%)	1/5 (20%)	3/3 (100%)

Conclusions: The majority (13/17; 76.47%) of those patients who had genomically low-risk and/or intermediate-risk disease did not receive CT despite positive lymph nodes (they were classified as high-risk according to MTB and were supposed to get CT). According to our limited data, additional information obtained by genomic RS might spare patients from unnecessary CT. MTBs are not keen to decide not to recommend CT based solely on classical clino-pathologic characteristics.

CONCORDANCE OF NEWLY DESIGNED CANCER-SPECIFIC MALNUTRITION SCREENING TOOL (GNP) AND WELL ESTABLISHED STANDARD NRS 2002; CROATIAN NESTED CROSS-SECTIONAL STUDY

8

Robert Šeparović[1], Ana Tečić Vuger[1], Andreja Jurić[1], Mirjana Pavlović[1], Žarko Bajić[2]

[1] Department of Medical Oncology, University Hospital for Tumors, Clinical Hospital Center "Sestre milosrdnice", Zagreb, Croatia

[2] Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia

Prevalence of malnutrition in cancer patients can be as high as 87%. Malnutrition may affect a cancer treatment and prognosis from the very beginning , through the course of illness. Good nutritional screening has to meet two conflicting requirements: it has to be accurate (valid, reliable - with low inter-observer variability, sensitive and specific) while feasible (speedy, inexpensive and non-invasive). Complexity of this demand may be one of the reasons why nutritional assessment is routine part of cancer care in minority of hospitals, why only 50% of malnourished cancer patients are recognized and only 58% receive nutritional support. The aim of our study was to check the concordance of Good Nutrition Practice (GNP) screening tool, newly designed for continuous tracking of cancer patients, and well established and currently recommended by European Society of Parenteral and Enteral Nutrition (ESPEN) but not cancer specific Nutritional Risk Screening - 2000 (NRS 2002), designed for ad - hoc usage only. This one – center nested cross - sectional study was done on the consecutive sample of general population of patients hospitalized for at least two days at Department of Medical Oncology, University Hospital for Tumors, University Hospital Center "Sestre milosrdnice", Zagreb, Croatia, between December 2015 and February 2016. Power analysis revealed that 42 subjects were needed to achieve 80% power at significance level of 0.05 using a one – sided non - inferiority test of correlated proportions when expected, reference NRS 2000 accuracy is 88%. The maximum allowed difference in GNP accuracy of predicting NRS 2000 result, that was still considered non - inferior was set at 15%. Anticipating up to 15% of missing data, the initial sample of 50 was recruited. Total of 50 patients were included, 26 (52%) of them female, 24 (48%) male, with mean (SD) age of 58 (11.3) years, and median (IQR) baseline body mass index (kg/m2) of 25 (22 - 28). By NRS 2000 we identified 17/50 (34%) and by GNP we identified 15/48 (31%) of patients as being in need for nutritional support. Overall percentage of agreement between two assessments (true positives + true negatives) was 40/48 (83%; 95% CI 69-92%). Overall agreement indicated by Cohen's Kappa was 0.63; 95% CI 0.30-0.82; p<0.001, and McNemar test didn't indicate significant differences between two screener's results (p=0.727). In conclusion, newly designed, cancer-specific screening tool (GNP) is concordant with NRS 2000 standard in detecting cancer patients with need for nutritional support.

CORRELATION OF BODY MASS INDEX AT DIAGNOSIS OF COLORECTAL CARCINOMA (CRC) AND TIME TO PROGRESSION TO METASTATIC OR RECURRENT DISEASE AFTER ADJUVANT TREATMENT

9

DAVOR AUGUST[3], Ana Tečić-Vuger[1], Mirjana Pavlović[1], Sanja Maloševac[4], Vesna Pavlica[2]

[1] Department for Medical Oncology, Clinical Hospital for Tumours, University Hospital Center „Sestre Milosrdnice“, Zagreb, Croatia

[2] Department for Clinical Pharmacology, Clinical Hospital for Tumours, Zagreb, Croatia

[3] Department for Internal medicine, Medical Oncology and Haemathology, General Hospital, Karlovac, Croatia

[4] Department for Internal medicine, Nephrology and Haemathology, General Hospital “Ivo Pedišić”, Sisak, Croatia

Studies have reported conflicting results on the association between body mass index (BMI) and prognosis of colorectal cancer (CRC). In recent retrospective analyses of early-stage CRC, low and high BMI scores were associated with worsened outcomes. Recent meta analysis found that being underweight before CRC diagnosis was associated with increased all-cause mortality and being obese (BMI ≥ 30 kg/m2) before cancer diagnosis was associated with increased CRC-specific mortality and all-cause mortality. On the other hand, being underweight, and class II/III obese (BMI ≥ 35 kg/m2) after diagnosis were associated with significantly increased all-cause mortality.

Individual data from 62 patients treated in Clinical Hospital for Tumors during period from 2010 to 2015, that progressed to metastatic disease or had a recurrent disease any time after surgery and completed adjuvant treatment, were pooled. We assessed BMI values at the begining of adjuvant treatment and progression-free survival (PFS) as time to development recurrent or metastatic disease, and we accounted for patient and tumor characteristics. All patients recieved adjuvant systemic treatment based on fluoropyrimidine protocol chemotherapy (5-FU/LV or capecitabin). According to BMI, patients were grouped into 3 classes: class I with normal BMI 20,0-24,99; class II with increased BMI 25-30; and class III were obese patients with BMI >30,00. Although analysis of variance has shown no statistically significant differences between the groups to the reached PFS (F=0,403; df=2/59; p=0,670) due to the relatively small sample of patients, results indicate nonlinear trend of association between BMI and PFS towards longer PFS in patients with normal BMI, and shortest PFS in obese patients. Age reached statistically significant negative correlation to PFS which indicates that younger patients had longer PFS. However, the significance of correlation is under strong influence of sample size, and these results can establish baseline for future investigation. In terms of prediction, correlation of age to PFS has shown that by every one year of older age, the PFS declines for 0,386 months.

We found high correlation between BMI and PFS indicating a trend that obese patients at the time of cancer diagnosis have shorter PFS, but to prove this effect, a larger number of patients for analysis is required. Age has negative correlation to PFS, one that reached stastical significance as younger patients had longer PFS, and is also a strong predictor: by every three years of older age, the PFS is one month shorter.

CORRELATION BETWEEN IMP3 EXPRESSION IN ADVANCED HIGH GRADE SEROUS OVARIAN CANCER WITH PLATINUM SENSITIVITY AND PATIENT SURVIVAL

10

Branka Petrić Miše[1], Nataša Lisica Šikić[4], Snježana Tomić[2], Dinka Šundov[2], Vesna Čapkun[3], Eduard Vrdoljak[1]

[1] Oncology, Clinical Hospital Centre Split, Split, Croatia

[2] Pathology, Forensic Medicine and Cytology, Clinical Hospital Centre Split, Split, Croatia

[3] Nuclear Medicine, Clinical Hospital Centre Split, Split, Croatia

[4] Pathology, Forensic Medicine and Cytology, General Hospital Zadar, Zadar, Croatia

Introduction: Majority of women with ovarian cancer continue to present themselves at advanced stages and the overall 5-year survival rate is around 45%. Standard approach in treatment of such patient population is platinum-based chemotherapy. Over the longer period we have not witnessed any significant improvement, either in treatment or in selection of patients for optimal therapy. Better understanding of the molecular and cellular markers is needed in predicting tumor progression and response to chemotherapy. The predictors of response to platinum-based chemotherapy can help to select sensitive patients for chemotherapy and to spare resistant ones from platinum-based chemotherapy toxicity. Accumulate evidence demonstrates that insulin-like growth factor II mRNA-binding protein (IMP3) has implicated in the tumor progression. IMP3 is an oncofetal protein involved in embryogenesis and its expression is associated with aggressive and advanced cancers because it promotes tumor cell proliferation, adhesion and invasion.

Objectives: To analyze correlation between expression of IMP3 in patients with advanced-stage high-grade serous ovarian carcinoma with platinum sensitivity and patient survival.

Methods: The expression of IMP3 was analyzed immunohistochemically in formalin-fixed, paraffin-embedded samples from 94 patients with advanced-stage high-grade serous ovarian cancer treated at the Clinical Hospital Centre Split and General Hospital Zadar, Croatia between January 1996 and January 2014. Positive staining was defined as brown staining in the cytoplasm. Negative staining was defined as absent staining or staining of less of 5% of tumor cells. The IMP3 expression was related to clinical features (stage according to the International Federation of Gynecology and Obstetrics (FIGO) and residual tumors after initial cytoreductive surgery), platinum sensitivity (according to platinum free interval (PFI) as platinum-refractory, platinum-resistant and platinum-sensitive) and patient progression free survival (PFS) and overall survival (OS).

Results: IMP3 immunoreactivity was not associated with FIGO stage (p=0.083), residual tumor after initial cytoreductive surgery (p=0,195), number of chemotherapy cycles (p=0,892), platinum sensitivity (p=0,851), patient PFS (p=0,114) and OS (p=0,519).

Conclusions: IMP3 as a marker has not predictive and prognostic value in patients with advanced-stage high-grade serous ovarian cancer.

CRIZOTINIB IN ADVANCED ALK-POSITIVE NSCLC – UPDATED RESULTS OF A RETROSPECTIVE MULTICENTER STUDY IN THE SLOVAK REPUBLIC

11

PETER BERZINEC[1], Peter Kasan[2], Lukas Plank[3], Igor Andrasina[4], Robert Godal[5], Juraj Mazal[6], Andrea Cipkova[4], Maria Cerna[7], Lucia Denkova[2], Gabriela Chowaniecova[1], Iveta Kuliskova[9], Helena Kuzmova[1], Marian Martak[2], Zuzana Pribulova[4], Maria Reckova[8], Milada Vesela[2]

[1] Oncology Department, Specialised Hospital of St Zoerardus Zobor, Nitra, Slovakia

[2] Oncology Department, University Hospital Bratislava, Bratislava, Slovakia

[3] Department of Pathology, Comenius University Jessenius Medical Faculty, Martin, Slovakia

[4] Oncology Department, East Slovakian Cancer Institute, Kosice, Slovakia

[5] Oncology Department, National Cancer Institute, Bratislava, Slovakia

[6] Pneumology Department, Faculty Hospital Banska Bystrica, Banska Bystrica, Slovakia

[7] Clinic of Pneumology and Phtiseology, Slovak Medical University, Bratislava, Slovakia

[8] Oncology Department, ADUS Polyclinic, Poprad, Slovakia

[9] Clinic of Pneumology and Phtiseology , University Hospital Martin, Martin, Slovakia

Background: Crizotinib has been available in Slovakia since October 2012 for the treatment of adults with previously treated ALK-positive advanced non-small cell lung cancer (NSCLC), based on the therapeutic indication approved by the European Medicines Agency. Purpose of this study was to assess the results achieved with crizotinib in the treatment of advanced NSCLC in clinical practice in Slovakia.

Methods: In this multicenter retrospective study, approved by the Ethical Committee of the Specialized Hospital of St Zoerardus Zobor, the data of 30 ALK-positive patients were reviewed. FISH with break-apart probes was used for the confirmation of ALK rearrangement in all cases. MedCalc® was used for the statistical analyses.

Results: Between October 2012 and August 2014, 20 out of 30 ALK-positive patients were treated with crizotinib. Ten patients did not receive crizotinib: five due to on-going first-line chemotherapy, five due to other reasons. Characteristics of the treated patients: M/W: 6/14, age (years) median 56, range 23-77, PS (ECOG/WHO): 0/1/2/3: 1/10/4/5, Histology: 19 patients adenocarcinoma, 1 NSCLC, NOS. Treatment results (data updated in March, 2016): RR was evaluated in 20 patients: PR + CR: 13 (12+1), 65% (95% CI: 41-85), SD: 3, 15% (95% CI: 3-38), PD: 3, 15% (95% CI: 3-38), NS: 1, 5%, DCR: 16, 80% (95% CI: 56-94), PFS: Kaplan-Meier estimate: 14 months (95% CI: 7 - 22), OS (with 45% of patients censored): 24 months (95%CI: 12 - 31), PS: significant improvement within 2 months (mean dif. –0.95, P = 0.0021), toxicities grade 3/4 occurred in 11 of 20 patients (55%), hematologic: 0, non-hematologic: hepatotoxicity 3/1, pneumonitis: 1/0, diarrhea 1/0, nausea: 3/0, vomiting: 1/1, vision disorder: 1/0, peripheral edema: 1/0, QT-interval prolongation: 1/0. Crizotinib was permanently discontinued due to toxicity in only two patients.

Conclusion: Treatment results seen in this retrospective study are encouraging and consistent with the published data from the prospective trials.

DIFFERENCES IN TREATMENT FAILURE BETWEEN PRIMARY AND SECONDARY METASTATIC COLORECTAL CANCER; CROATIAN PROSPECTIVE COHORT STUDY

12

Hrvoje Silovski[1], Mirjana Pavlović[2], Ana Tečić Vuger[2], Tajana Silovski[2], Žarko Bajić[3]

[1] Department of Surgery, University Hospital Center Zagreb, Zagreb, Croatia

[2] Department of Medical Oncology, University Hospital for Tumors, Clinical Hospital Center "Sestre milosrdnice", Zagreb, Croatia

[3] Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia

Colorectal cancer is the third most often cancer in Europe, just behind breast and prostate cancer. At the time of diagnosis 20% of patients have advanced illness. Risk of recurrence during the first 18 months from surgery is 18%. The objective of our study was to find whether there are differences in treatment failure between primary and secondary (patients previously treated with adjuvant systemic antineoplastic protocols) metastatic colorectal cancer. This post-marketing, open label, prospective cohort study enrolled patients from April 1, 2013 to March 31, 2014. We followed patients for 12 months. The last follow up exam was at March 31, 2015. The study was done at Department of Medical Oncology, University Hospital for Tumors, Zagreb University Hospital Center "Sestre milosrdnice", Zagreb, Croatia. Targeted population was the general population of patients diagnosed with metastatic colorectal cancer, with ECOG status <2. We included the consecutive sample of all patients initiated to bevacizumab during the enrollment period. Total of 128 patients were included, but 19 (15%) of them were lost for follow up during the 12 months. Out of remaining 109 patients, time of metastases was not properly recorded for 8 (7%) patients. The final sample size was 101 patients, 60 (59%) of them male, 41 (41%) female. Median (interquartile range) age was 60 (54-67) years. Patients with primary metastatic disease were somewhat more often male; patients with secondary metastatic disease female. Patients with secondary metastatic disease had larger body mass index. Approximately one third of them were obese (BMI≥30.0). Total number of bevacizumab cycles was significantly larger in primary metastatic disease group. The overall proportion of treatment failure was not significantly different between primary and secondary metastatic colorectal cancer. Treatment success was achieved in 23% and 25% of patients respectively. But the causes of treatment failure were different. Primary metastatic group, significantly more often than secondary metastatic group, experienced illness progression during the first 12 months from diagnosis (P=0.040; ϕ=0.20). In secondary metastatic group, significantly more often than in primary metastatic group, systemic therapy was not indicated because of low performance status (P=0.027; ϕ=0.22). Causes of treatment failure are different in patients with primary or secondary metastatic disease.

DIFFERENCE IN EFFICACY OF FULVESTRANT 250 MG AND 500 MG ON ESTROGEN POSITIVE ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN IS MODERATED BY BASELINE BODY MASS INDEX; CROATIAN PROSPECTIVE COHORT STUDY

13

Ana Tečić Vuger[1], Mirjana Pavlović[1], Tajana Silovski[1], Robert Šeparović[1], Žarko Bajić[2]

[1] Department of Medical Oncology, University Hospital for Tumors, Clinical Hospital Center "Sestre milosrdnice", Zagreb, Croatia

[2] Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia

Fulvestrant's pharmacokinetic profile was not found to be affected by body weight. However, recent Italian study found that increased body mass index (BMI) is associated with lower fulvestrant clinical benefit rate (CBR). To our best knowledge, no study so far has reported differences in efficacy of two fulvestrant dosages depending on patients' body mass at the time of fulvestrant initiation. Objective of our study was to find out whether fulvestrant 250 mg and 500 mg difference in progression free survival of postmenopausal women with estrogen positive advanced breast cancer is associated with patients' baseline body mass index. This post - marketing, open label, prospective cohort study was done on the consecutive sample from population of postmenopausal women with locally advanced or metastatic, estrogen receptor positive breast cancer, treated by fulvestrant at Department of Medical Oncology, University Hospital for Tumors, University Hospital Center "Sestre milosrdnice", Zagreb, Croatia, from January 2010 to June 2015. Data were analyzed by Cox regression. Final sample consists of 43 patients treated by fulvestrant 250 mg, and 66 patients treated by fulvestrant 500 mg. Patients treated by different dosages were comparable by demographic, vital and clinical characteristics, except that patients on fulvestrant 500 mg had more widespread metastases. After adjustment for age, number and localization of metastases, number of adjuvant chemotherapy and hormonal therapy lines before the introduction of fulvestrant, neither dose nor BMI were significantly associated with PFS. But their interaction was significant and clinically relevant. Median PFS was lowest in overweight patients on fulvestrant 250 mg (3 months), and highest in overweight patients on fulvestrant 500 mg (11 months). In conclusion, difference in fulvestrant 250 mg and 500 mg efficacy is moderated by BMI. Fulvestrant 250 mg PFS does not change with BMI. Fulvestrant 500 mg PFS changes significantly with BMI.

FIRST-LINE CHEMOTHERAPY WITH PACLITAXEL AND PLATINUM SALT INDUCES MACROCYTOSIS IN EPITHELIAL OVARIAN CANCER PATIENTS

14

Tihana Boraska Jelavić[1], Toni Boban[2], Luka Brčić[3], Eduard Vrdoljak[1]

[1] Department of Oncology, University Hospital Split, Split, Croatia

[2] School of Medicine, University of Split, Split, Croatia

[3] Department of Medical Biology, School of Medicine, University of Split, Split, Croatia

Introduction: First-line treatment for epithelial ovarian (OC), fallopian tube (FTC) and primary peritoneal cancer (PPC) is combination chemotherapy with paclitaxel and platinum salt (cisplatin or carboplatin), (TP). Based on a clinical observation that patients receiving this therapy develop macrocytosis we conducted a clinical research to investigate this observation and explore possible predictive role of macrocytosis on response rate (RR), progression- free (PFS) and overall survival (OS) in OC, FTC and PPC patients.

Materials and Methods: We retrospectively collected laboratory and clinical data of OC, FTC and PPC patients treated in a single centre, Department of Oncology, Clinical Hospital Split, from 2004 till 2015. Patients diagnosed with epithelial OC, FTC and PPC, FIGO stage IC or higher, treated with first-line TP chemotherapy and with complete blood count records available were eligible for our analysis. Macrocytosis was defined as an increase of mean corpuscular volume (MCV) of peripheral red blood cells above 97.2 fl during the treatment and 30 days after the last chemotherapy cycle.

Results: A total of 184 patients were enrolled in this study. Amongst them, 141 patients were treated with 3-weekly schedule (platinum salt and carboplatin on day 1 of every 3-week cycle), while 43 patients were treated with „dose dense“ schedule (platinum salt on day 1 every 3 weeks and paclitaxel on day 1 every week). Macrocytosis was induced in 35% of patients, overall. In patients treated with 3- weekly schedule it was induced in 26% of cases and in patients treated with „dose dense“ schedule in 67% (p=1.29 x 10-6). Macrocytosis was not correlated with RR, PFS and OS in patients treated with 3- weekly schedule, but it was significantly correlated with PFS in patients treated with „dose dense“ schedule (median PFS of 24.6 months (MCV ≥ 97.2) vs 15.3 months (MCV < 97.2); HR = 0.42, 95% CI = 0.18-0.94 , P=0.036). At the multivariate analysis, macrocytosis and stage of the disease were significant independent predictors of better PFS.

Conclusion: Combination chemotherapy with TP in OC, FTP and PPC patients induces macrocytosis significantly more often in those treated with „dose dense“ than 3-weekly schedule. In patients treated with „dose dense“ schedule it can be predictive for longer PFS. This finding should be confirmed on a larger group of patients in a prospective study.

FULVESTRANT 500 MG IS MORE EFFECTIVE THAN FULVESTRANT 250 MG IN REAL-LIFE CLINICAL SETTINGS; CROATIAN PROSPECTIVE COHORT STUDY

15

Ana Tečić Vuger[1], Mirjana Pavlović[1], Tajana Silovski[1], Robert Šeparović[1], Žarko Bajić[2]

[1] Medical oncology, University Hospital for Tumors, Clinical Hospital Center "Sestre milosrdnice", Zagreb, Croatia

[2] Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia

CONFIRM, phase III randomized controlled trial, has shown statistically significant and clinically relevant superiority of fulvestrant 500 mg over 250 mg (HR=0.80; 95% CI 0.68-0.94) with median PFS times of 6.5 and 5.5 months respectively. Objective of our study was to compare efficacy of two mentioned fulvestrant dosages in real - life conditions. This post - marketing, open label, prospective cohort study was done on the consecutive sample from population of postmenopausal women with locally advanced or metastatic, estrogen receptor positive breast cancer, treated by fulvestrant at Department of Medical Oncology, University Hospital for Tumors, University Hospital Center "Sestre milosrdnice", Zagreb, Croatia, from January 2010 to June 2015. Final sample consists of 43 patients treated by 250 mg, and 66 patients treated by 500 mg. Patients treated by different dosages were comparable by demographic, vital and clinical characteristics, except that patients on fulvestrant 500 mg had more widespread metastases. Univariate analysis proved superiority of larger dosage (HR=0.58; 95% CI 0.36-0.91; p=0.019) with median PFS times of 3.0 (95% CI 2.4-3.6) months and 6.0 (95% CI 4.5-7.5) respectively. After adjustment for age, number and localization of metastases, number of adjuvant chemotherapy and hormonal therapy lines before the introduction of fulvestrant and body mass index, HR changed to 0.50 (95% CI 0.27-0.91; p=0.024). Our study proved the superiority of fulvestrant 500 mg over fulvestrant 250 mg in real - life clinical settings.

GENE EXPRESSION PROFILING OF TUMOR-INITIATING STEM CELLS IN RENAL CELL CARCINOMA

16

Anna M. Czarnecka[1], Mohammed I. Khan[1], Michal Fiedorowicz[2], Jaroslaw Orzel[2, 3], Marlena Welniak-Kaminska[2], Damian Strzemecki[2], Zbigniew Rogulski[4], Magdalena Krol[5], Cezary Szczylik[1]

[1] Department of Oncology with Laboratory of Molecular Oncology, Military Institute of Medicine, Warsaw, Poland

[2] Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

[3] Faculty of Electronics and Information Technology, Warsaw University of Technology, Warsaw, Poland

[4] Faculty of Chemistry, Warsaw University, Warsaw, Poland

[5] Faculty of Veterinary Medicine, Warsaw University of Life Sciences, Warsaw, Poland

Background: Cancers originate from stem cell-like cells that share many characteristics with normal stem cells, including ability of self-renewal, pluripotent differentiation, resistance to therapy and are highly metastatic. In renal cell cancer - cancer stem cells have been primarily isolated based on expression of putative mesenchymal stem cell markers endoglin (CD105) and prominin-1 (CD133).

Aim: This study was designed to characterize endoglin positive RCC cells and evaluate these cells as potential tumor initiating cancer stem-like cells.

Material and Methods: Primary and stable RCC cell lines – derived from primary and metastatic tumors - were used for analysis. Mesenchymal stem cell markers expression - including CD11b, CD19, CD24, CD34, CD44, CD45, CD73, CD90, CD146, HLA-DR and ALP - were analyzed. After initial candidate cell line screening, CD105 expressing cells were isolated from ACHN (metastatic RCC) and CAKI-2 (primary RCC) cell lines (FACSAriaII) for further analysis. Soft agar colony formation assay was used confirm in vitro clonogenic potential of candidate cells. CD105(+) and CD105(-) cells were injected subcutaneously into the NOD/SCID mice to confirm tumorigenic potential in vivo. Agilent human gene expression 4x44K microarray was used for gene expression analysis. Animals were scanned with Bruker 7T Biospec MRI and Bruker Albira PET/SPECT/CT imaging system.

Results: Endoglin and promonin expressing cells were found in primary and metastatic tumor derived RCC cell lines. Endoglin expressing subpopulation is abundant in metastatic cell lines. CD105(+) but not the CD105(-) population show high tumorigenicity when injected in immunodeficient (SCID) mice. CD105(-) cells derived tumors were significantly smaller than CD105+ or unsorted cells derived tumors and had lower FDG uptake. CD105+ cells co-express other mesenchymal stem cell markers (i.e. CD90, CD73 and CD44). CD105(+) cells shown deregulation of Wnt/β-catenine signaling, epithelial-mesenchymal transition pathway and TGF-β signaling. Major transcriptional regulators controlling survival of RCC-CD105(+) cells shown are TNF, TGFB1, ERBB2.The complementary gene-set analysis identified three significant gene set: genes involved in Rap1, PI3K-Akt and Hippo signaling pathways as showing a strong significant enrichment.

Conclusions: CD105(+) cells derived from renal cell cancer are tumor-initiating cells with stem characteristics. Our results indicate the presence of a stem-like mesenchymal cell population resident in human renal tumors that may have a role in the pathophysiological cancer cell turnover, metastasis and/or in response to therapy. Endoglin and TGF beta pathway may be considered as targets for novel RCC therapies.

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HYPOFRACTION RADIOTHERAPY AFTER BREAST CONSERVING SURGERY IN MONTENEGRO-AN EVULATION OF CLINICAL EXPIRINCE

17

Svetlana Corsovic[1], Vanja Karadjinovic[1], Vesna Plesinac Karapandzic[2]

[1] Radiotherapy, Clinic of oncology and radiotherapy, Podgorica, Montenegro

[2] Radiotherapy, Institute of Oncology and radiotherapy, Belgrade, Serbia

Background and purpose: The aim of this retrospective study is to evaluate the incidence of local recurrence, acute and late toxicity of skin, overall survival and assessment of the effects of treatment in relation to axillary lymph node status.

Material and methods: Between 2007-2009, 86 patients with pTis-pT1,pT2,No-N2 breast cancer underwent radiotherapy treatment after conservative surgery the Clinical of Oncology and radiotherapy in Podgorica. The dose delivered was 50 Gy given in 15 fractions over 20 days (3, 3 Gy daily fraction). In the 23 (26,7%) patients with high risk of relapse was treated with radiotherapy of supraclavicular region with 45Gyin 15 fractions over 42 days.Radiotherapy –related complications were categorized using the RTOG Late Radiation Morbidity Scoring Criteria.

Results: Median of follow up was 6 years. Among 86 patients 2,3% of patients (2/86) had relapsed. Considering the acute toxicity we found that 27 (31,4%)patients had grade 0; 26 (30,2) patients had grade 1 ; 27(31,4%) had grade 2 and 6 (7%) patients had grade 3. Considering the late toxicity we found that 36 (41,9%) patients had grade 0; 30 (34,9%)patients had grade1; 17(19,8%)had grade2 late toxicity and 3(3,5 %) had grade3 late toxicity. Cox uni-variate regression analysis showed that lymph node metastasis is the independent prognostic factor (95% confidence interval ,1.2-5.7; p=0,019).

The 5- years was overall survival was 90, 6%.

Conclusion: Hypofractionated RT is an effective treatment in terms of local control in patients with early breast cancer with acceptable level of occurrence of acute and late skin toxicity and shown equivalent rates of overall survival. The status of axillary lymph node is the most important prognostic factor in our study.

Key words: breast cancer, hypofraction radiotherapy,axillary nodes

INTEGRATION OF PRECISION ONCOLOGY IN THE TREATMENT OF GASTROINTESTINAL TUMORS

18

Istvan PETAK[1, 2], Csilla HEGEDUS[1], Edit VARKONDI[1], Andrea KOHANKA[1], Richard SCHWAB[1], Gyorgy BODOKY[3]

[1] Laboratory, R&D, Oncompass Medicine Hungary, Budapest, Hungary

[2] Medical Chemistry, Semmelweis University, Budapest, Hungary

[3] Oncology, St. László Hospital, Budapest, Hungary

Precision medicine aims to incorporate individual molecular genetic profiles in cancer treatment decisions in order to match patients with the best available therapeutic options. Increasing body of evidence associates cancer gene mutations and copy number alterations with cancer prognosis and therapeutic response. Here, we present the results and clinical relevance of multiplex genetic testing of 48 Hungarian patients with gastrointestinal cancer.

In our pilot program in 2015, 34 patients with colorectal cancer, 10 patients with pancreatic cancer and 4 patients with gastric cancer were profiled using a 58-gene hotspot gene panel and next-generation sequencing (NGS). Copy number alterations of relevant driver genes were investigated with fluorescent in situ hybridization (FISH). Based on available scientific evidence, the identified genetic alterations were classified as drivers, variants of unknown significance (VUS) or single nucleotide polymorphisms (SNP) and were associated with on-label, off-label targeted drugs and relevant targeted compounds available in clinical trials. Therapy access of patients was assisted upon individual physician's request. Molecular profiling of tumor tissue samples followed by molecular, clinical interpretation of the obtained cancer genetic profiles and Molecular Tumor Board consultations were individually reimbursed by the National Health Insurance Fund of Hungary.

In the total cohort of patients, 113 driver gene alterations were identified (79% in colorectal, 18% in pancreatic and 3% in gastric cancer patients). The number of drivers simultaneously present in the same tumor sample varied between 0 and 7. Positively associated targeted on-label, off-label drugs and clinical trials matching with both the molecular and the clinical profile were identified in 27%, 94% and 83% cases, respectively (27%, 100%, 91% of colorectal cancer cases; 40%, 100%, 80% of pancreatic cancer cases and 0%, 25%, 25% of gastric cancer cases, respectively). Based on the tumor molecular profile, presumably ineffective but otherwise registered drugs were also identified in 60% of the cases.

The individually reimbursed pilot program described here clearly establishes that the precision oncology approach can be successfully delivered to the clinic and efficiently helps finding the best individualized treatment options for cancer patients.

INTERACTION OF ESTROGEN AND PROGESTERONE RECEPTORS AND BODY MASS INDEX SIGNIFICANTLY CHANGES THE TREATMENT OUTCOME IN HER2+ BREAST CANCER TREATED BY ENDOCRINE THERAPY AND TRASTUZUMAB; CROATIAN NESTED CROSS-SECTIONAL STUDY

19

Mirjana Pavlović[1], Ana Tečić Vuger[1], Tajana Silovski[1], Andreja Jurić[1], Žarko Bajić[2]

[1] Department of Medical Oncology, University Hospital for Tumors, Clinical Hospital Center "Sestre milosrdnice", Zagreb, Croatia

[2] Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia

Several studies indicated that estrogen receptor positive and progesterone receptor negative breast cancer patients have worse prognosis than patients with progesterone receptor positive tumors, but progesterone receptor status was not proven to be important predictive factor. The objective of our study was to find out whether there are demographic or clinical factors that may improve progesterone predictive validity in patients with estrogen and HER2 receptor positive breast cancers. This one-center, post-marketing, open label, nested cross-sectional study enrolled patients from June 2012 to March 2015. The study was conducted at Department of Medical Oncology of University Hospital for Tumors in Zagreb. Targeted population was the general population of patients with HER2 and estrogen receptor positive breast cancer, ECOG status 0 or 1, adjuvantly treated with trastuzumab and endocrine therapy. We included the consecutive sample of all patients who started trastuzumab and endocrine therapy during the enrollment period. Total of 128 estrogen and HER2 receptor positive patients were included. Median (IQR) age was 63 (51-67) years. 45 (37%) patients had normal body mass index (≤ 25.0 kg/m2), while 38 (31%) were obese (≥30.0 kg/m2). Progesterone positive receptors were present in 100 patients (78%). Body mass index was comparable in patients with estrogen and progesterone receptor positive or negative tumor. In patients with normal body mass index (<25.0 kg/m2) there was no statistically significant nor clinically relevant difference in illness progression between patients with progesterone receptor positive (11% progression) and progesterone receptor negative (6% progression) tumors (P=0.584). The same was found in overweight patients (body mass index 25.0-29.9 kg/m2) where progesterone receptor positive patients had 0% progression, and progesterone negative 11% progression (P=0.281). However, in obese patients with body mass index ≥30.0 kg/m2, progression of disease was found in 57% of patients with progesterone receptor negative, and in only 7% of patients with progesterone receptor positive tumors (P=0.001). Odds for disease progression were 21 times larger (OR=21.3; 95% CI 2.69-168.9; P=0.004) in patients with negative progesterone receptors and body mass index ≥30. Probability of disease progression was 96% in these patients. In conclusion, interaction of estrogen, progesterone and body mass index significantly changes the treatment outcome in HER2+ breast cancer treated by endocrine therapy and trastuzumab

INTERACTION OF HORMONE RECEPTORS AND BODY MASS INDEX IS IMPORTANT PREDICTOR OF DISEASE PROGRESSION IN HER2+ BREAST CANCER PATIENTS TREATED BY TRASTUZUMAB; CROATIAN NESTED CROSS-SECTIONAL STUDY

20

Sanja Maloševac[1], Ana Tečić Vuger[2], Mirjana Pavlović[2], Andreja Jurić[2], Žarko Bajić[3]

[1] Department for nephrology and hematology, General hospital Sisak, Sisak, Croatia

[2] Department of Medical Oncology, University Hospital for Tumors, University Hospital Center "Sestre milosrdnice", Zagreb, Croatia

[3] Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia

Several studies, including our own previous analysis, indicated that estrogen receptor positive and progesterone receptor negative breast cancer patients have worse prognosis than the patients with progesterone receptor positive tumors, but progesterone receptor status was not proven to be important predictive factor. Our previous analysis indicated significant contribution of body mass index to the interaction of estrogen and progesterone receptors in HER2 positive, estrogen receptor positive breast cancer treated with endocrine therapy and trastuzumab. Objective of our study was to examine the contribution of body mass index to the known effect of estrogen/progesterone receptor interaction in prediction of disease progression in all patients treated with trastuzumab regardless of estrogen receptor status. This one-center, post-marketing, open label, nested cross-sectional study enrolled patients from June 2012 to March 2015. Enrollment was ended on March 13th 2015. The study was conducted at the Department of Medical Oncology of University Hospital for Tumors in Zagreb, Croatia. Targeted population was the general population of patients with HER2 positive breast cancer, ECOG status 0 or 1, adjuvantly treated with trastuzumab. We included the consecutive sample of all patients initiated with trastuzumab during the enrollment period. Total of 225 patients were included. Their median age was 60 (52-67) years. Their median body mass index was 26 (23-30) kg/m2. Tumors had positive estrogen receptors in 61.8% and positive progesterone receptors in 49.3% of patients. At the time of diagnosis 12.7% of patients had metastatic disease. 17.9% of patients experienced disease progression. In patients with normal BMI (≤24.9 kg/m2) and in overweight patients (25.0-29.9 kg/m2) interaction of progesterone/estrogen receptors was not significant predictor of disease progression (p=0.198 and p=0.427 respectively). In both groups disease progression was most frequently noted in patients with negative both hormone receptors. However, in obese patients (≥30.0 kg/m2) disease progression was most frequently noted (57.1%) in patients with estrogen positive and progesterone negative tumors (p=0.004). In conclusion, the estrogen/progesterone interaction is important predictor of disease progression in obese patients treated with trastuzumab.

IS IT ECONOMICALLY BENEFICIAL TO USE IHC AS UPFRONT EGFR DETECTION METHOD IN ADVANCED NSCLC?

21

Nina Turnšek Hitij[1], Izidor Kern[1], Aleksander Sadikov[2], Lea Knez[1], Tanja Cufer[1]

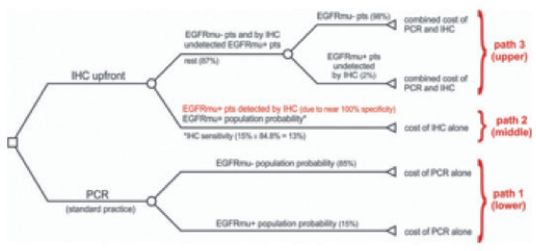
[1] Medical Oncology Unit, University Clinic Golnik, Golnik, Slovenia

[2] Department of Artificial Intelligence, Faculty of Computer and Information Science, Ljubljana, Slovenia

Background: PCR detected common EGFR activating mutations (exon 19 deletion, L858R mutation) best predict response to EGFR tyrosine kinase inhibitors (EGFR TKI) in advanced NSCLC. Immunohistochemistry (IHC) with mutation-specific antibodies is an alternative method for common EGFR mutation (EGFRmu) detection. IHC is less expensive and more rapid compared to PCR, however, it has limited sensitivity due to the intrinsic limitation of being able to detect only 65% of all exon 19 deletions. Due to limited sensitivity IHC cannot replace current standard PCR. But, it might be used as an upfront EGFRmu test followed by PCR in IHC EGFRmu negative cases. Therefore, we evaluated the acceptable ratio of PCR and IHC costs that do not lead to increased expenses, based on the EGFR activating mutation rate observed in different populations.

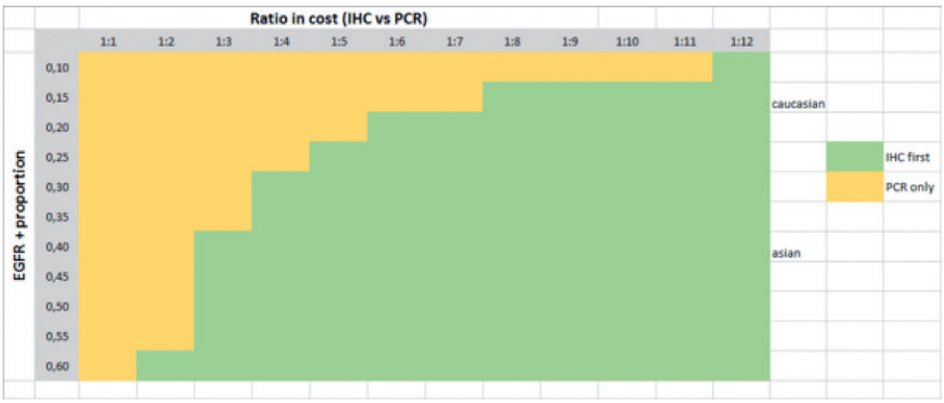
Methods: Decision tree methodology from the decision analysis field was used for the analysis of cost-effectiveness and potential side-by-side usage of both methods, PCR and IHC. Decision tree corresponding to three possible situations is represented in Figure 1. Our previous results for the accuracy of IHC EGFRmu determination (overall 85% sensitivity and 100% specificity, for combined del19 and L858R) were used for the analysis.

Fig. 1: Decision tree process for determining under which conditions upfront EGFR mutation testing with IHC would be economically preferable before PCR testing.



Results: We varied the percentages of truly EGFRmu positive patients in the population known to be considerably different in various populations (approximately 15% in Caucasian and 40% EGFRmu positive NSCLC in Asian population). As demonstrated in Figure 2, considering Caucasian population, the ratio in costs needs to be about eight-to-one (IHC eight times cheaper than PCR) for upfront IHC testing to be economically justified. However, when increasing the percentage of EGFRmu, this cost ratio might change significantly, as for Asian population, this ratio drops to only between four-to-one and three-to-one.

Fig. 2: Cost ratio between IHC and PCR in correlation to the proportion of EGFR mutations in a given population



Discussion: Based on our analyses, upfront IHC EGFRmu testing might be economically justifiable in populations with higher rate of EGFRmu, such as Asian populations, but not in Caucasian populations. However, IHC EGFRmu testing may still play important role in developing countries without access to PCR and in developed countries adopting NGS as standard, thus allowing majority of EGFRmu positive patients an early access to targeted therapy.

LATER INTRODUCTION OF BEVACIZUMAB IS INDEPENDENT PREDICTOR OF METASTATIC COLORECTAL CANCER PROGRESSION; CROATIAN PROSPECTIVE COHORT STUDY

22

Mirjana Pavlović[1], Ana Tečić Vuger[1], Tajana Silovski[1], Andreja Jurić[1], Žarko Bajić[2]

[1] Department of Medical Oncology, University Hospital for Tumors, Clinical Hospital Center "Sestre milosrdnice", Zagreb, Croatia

[2] Healthcare Research, Biometrika Healthcare Research, Zagreb, Croatia

Colorectal cancer is the third most common cancer in Europe. At the time of diagnosis 20% of patients have advanced disease. Risk of recurrence during the first 18 months after surgery is 18%. Bevacizumab prolongs progression free and overall survival in metastatic colorectal cancer. The objective of our study was to determine whether the time of introduction of bevacizumab affects the time to progression of metastatic disease in real-life clinical settings. This post-marketing, open label, prospective cohort study enrolled patients from April 1st 2013 to March 31st 2014. Follow-up period was 12 months and the last follow up exam was on March 31st 2015. The study was conducted at Department of Medical Oncology of University Hospital for Tumors in Zagreb. Targeted population was the general population of patients diagnosed with metastatic colorectal cancer, with ECOG status <2. We included the consecutive sample of all patients who started bevacizumab during the enrollment period. Total of 128 patients were included, 19 (15%) of them were lost from follow up during the 12 months period and the time of diagnosis of metastatic disease was not properly recorded for 8 (7%) out of remaining 109 patients. The final sample size was 101 patients (59% were male and 41% female). Median age was 60 (54-67) years.

Bevacizumab was initiated at median of 68 (46-111) days from diagnosis of metastatic disease. Disease stage at the time of diagnosis was the only variable significantly associated with the time from diagnosis of metastatic disease to initiation of bevacizumab (Jonckheere-Terpstra test, standardized J-T=-2.34; P=0.019). Initiation of bevacizumab was the most delayed in patients with DUKES' A and B stages and earliest in patients with DUKES' C which could be explained with earlier and more specific diagnostic workup in patients with more advanced disease at the presentation. After adjustment by multivariate binary logistic regression, time from diagnosis of metastatic disease to initiation of bevacizumab was statistically significant independent predictor of illness progression during the first 12 months. Other significant independent predictors of illness progression were age and disease stage at diagnosis; older patients had lower odds for progression and higher the tumor stage at the diagnosis higher the risk of disease progression. In conclusion, our study has shown, in real-life clinical settings, that the time from diagnosis of metastatic disease to the initiation of bevacizumab is associated with higher risk of metastatic colorectal cancer progression within the first 12 months.

OVERVIEW: EXPERIENCE GAINED IN THE REIRRADIATON OF THE HEAD AND NECK CANCER

23

Veronika Drajkó[1], Timea Klinkó[1], Csilla Katona[1], László Landherr[1]

[1] Central Department of Oncoradiology, Uzsoki Hospital, Teaching Hospital of Semmelweis University Faculty Of Medicine, Budapest, Hungary

Purpose: Thanks to the hard struggle oncologists, radio-oncologists and surgeons today is not surprising that with previously treated patients with head and neck cancer surviving long and appears a local recurrent or second primary cancer in a previously irradiated area. A lot of questions arise in connection with reirradiation. Our presentation is based on an article published in 2013 by Primoz Strojan et al. They analyzed the literature of reirradiation for previously irradiated patients with head and neck cancer of non-nasopharyngeal origin.

Methods: I grouped the studies according to the radiotherapy technique used for reirradiation. I examined the number of patients, the interval to reirradiation, the tumor dose, the fractions, the reirradiated area, the post-surgical status, the concurrent systemic treatments, the late toxicity and the outcome (overall survival (OS), local control (LC), loco-regional control (LRC)).

Results: With modern radiotherapy techniques (IMRT, SBRT), with adequate imaging support (CT, PET/CT) and with improved dose distribution may improve local control and reduce toxicity of reirradiation. The reirradiation alone and combination with concurrent systemic therapy is feasible and tolerable. In properly selected patients offering a meaningful survival, in the range of 10% to 30% at 2 years. Whenever feasible, salvage surgery is the method of choice for curative intent. Based on studies actually we can get the best effect with multidisciplinary treatments.

Conclusion: Because of the diversity of the studies – different radiotherapy techniques, tumor doses, surgical radicality, chemotherapy drugs, elapsed time to reirradiation - we can't conclude consistent results. We should strive to coordinate national and international practice.

PD-L1 EXPRESSION IN TUMOR CELLS AND IMMUNE CELLS IN NSCLC

24

Urška Janžič[1], Izidor Kern[3], Andrej Janžič[2], Tanja Čufer[1]

[1] Department of Medical Oncology, University Clinic Golnik, Golnik, Slovenia

[2] Chair of Social Pharmacy, University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

[3] Department of Pathology, University Clinic Golnik, Golnik, Slovenia

Keywords: PD-L1 expression, NSCLC, tumor cells, immune cells

Background: Immune checkpoint inhibitors are becoming the new standard of treatment for NSCLC. There is a need for predictive biomarker since only about 25% of patients respond to this therapy. PD-L1 has shown to be the most promising biomarker so far. We assessed the expression of PD-L1 in tumor cells (TCs) and in immune cells (ICs) of lung adenocarcinoma (AC) and squamous-cell carcinoma (SCC).

Methods: We obtained FFPE from 54 surgically resected NSCLC tumors. PD-L1 expression was assessed in TCs and ICs by immunohistochemistry using antibody SP142 (Ventana, USA). We used a preplanned cut-off value of 5% to determine PD-L1 positivity on either TCs or ICs, regardless of the intensity.

Results: Among 54 surgically removed tumor samples only 20 % of samples did not express PD-L1, nor in TC nor in ICs. Major difference was noted in AC between TC and IC, 17% vs. 72% (p<0.001). On the other hand, in SCC, PD-L1 positivity was 52% and 76% in TC and IC (p=0.146), respectively. Combined PD-L1 positivity was high in both histological subtypes, especially because of IC positivity. When IC was characterized as PD-L1 positive, the TC of the same tumor sample was positive, too.

Conclusion: Although small, our series shows the importance of the type of cells selected for PD-L1 positivity determination. The expression of PD-L1 in IC seems to be more prominent than in TC.

	Tumor specimens N	TC or IC N (%)	TC N (%)	IC N (%)	p value (TC vs IC)
Total	54	43 (80)	18 (33)	40 (74)	
Adenocarcinoma	29	21 (72)	5 (17)	21 (72)	**<0.001**
Squamous cell carcinoma	25	22 (88)	13 (52)	19 (76)	0.146
p value (histology)		0,281	**0.016**	0.764	

RETROSPECTIVE ANALYSIS OF EFFICACY OF TRASTUZUMAB IN ADJUVANT TREATMENT OF HER 2 POSITIVE EARLY BREAST CANCER – SINGLE INSTITUTION EXPERIENCE

25

Marija Ban[1], Jelena Viculin[1], Snježana Tomić[2], Vesna Čapkun[3], Ante Strikić[1], Branka Petrić Miše[1], Ivan Utrobičić[4], Eduard Vrdoljak[1]

[1] Department of Oncology, University Hospital Split , Split, Croatia

[2] Department of Pathology, University Hospital Split , Split, Croatia

[3] Department of Nuclear medicine, University Hospital Split , Split, Croatia

[4] Department of Surgery, University Hospital Split , Split, Croatia

Background: Trastuzumab added to chemotherapy is the cornerstone of adjuvant treatment of early HER2 positive breast cancer. Clinical trials and metaanalyses of adjuvant trastuzumab have shown significant reduction in risk of recurrence and death. Nevertheless, the real magnitude of the effect of any drug must be reevaluated in daily clinical conditions, due to the fact that daily clinical practice often differs from conditions in clinical trials.

Patients and methods: In order to measure the benefit of adding adjuvant trastuzumab in HER 2 positive early breast cancer treatment, we have performed retrospective analysis in a single institution on consecutive patients divided in 2 cohorts: one, treated in "pre - trastuzumab" and the other in "trastuzumab era". Between 2003 and 2012, 258 consecutive HER 2 positive patients with early breast cancer have been treated with adjuvant chemotherapy, 103 patients did not received trastuzumab (patients treated from 2003 till 2007), and 155 received trastuzumab (patients treated from 2008 till 2012).

Results: Patients who received trastuzumab experienced significantly longer median disease-free survival (107 vs. 92 months, LR: 11.6, $p < 0.001$); breast cancer-specific survival (130 vs. 117 months, LR: 10.7, $p < 0.001$) and median overall survival (123 vs. 108 months LR = 11.6, $p < 0.001$). The benefits of adding trastuzumab were independent of chemotherapy regimen and hormonal therapy.

Conclusion: This retrospective analysis has shown a clear, statistically significant benefit of adjuvant trastuzumab in treatment of early, HER2 positive breast cancer in daily clinical practice, and confirmed the results of the registration clinical trials.

Keywords: Early breast cancer, HER2, Adjuvant chemotherapy, Trastuzumab, Retrospective analysis

RETROSPECTIVE ANALYSIS TREATING HEPATOCELLULAR CARCINOMA. SIX YEAR, SINGLE CENTER EXPERIENCE.

26

Gyula Demeter[1], Gábor Lakatos[1], Ágota Petrányi[1], Marianne Farkas[1], Éva Végh[1], György Bodoky[1]

[1] Oncology, United St. István and St. László Hospital, Budapest, Hungary

Background: Hepatocellular carcinoma is the most common type of liver cancers worldwide. Major risk factors for HCC are viral hepatitis, alcohol abuse and metabolic disorders. Curative therapeutic modalities are surgical resection and liver transplantation. Locoregional ablation and sorafenib remain palliativ modalities.

Aim: to summarize data about epidemiology, etiology, treatment modalities, survival of patients with HCC in our center

Patients and methods: Data from HCC patients from the Department of Oncology of St. Laszló Hospital between February 2010 and April 2016 have been collected and were assessed retrospectively.

Results: 203 patients with HCC were enrolled into the analysis. Mean age was 65 year, 75.8% men, 24.1% women. Viral hepatitis was noted in 43.4% of the patients; alcohol abuse and steatohepatitis occured in 47.6% and 5.7% respectively. Most frequent comorbidities were diabetes mellitus (37.8%) and hypertension (42.8%). Diagnosis was made during follow up for hepatitis in only 21.4%. 16.2% of all patients was in BCLC A stage, 33.9% in B, 44.3% in C and 4.9% in D stage. 17.7% of patients had undergone hepatic resection, 27% had locoregional therapy, 73.8% was treated with sorafenib (most patients were in Child-Pugh A stage, only 13.2% were in stage B) and 56% of this group was enrolled in a clinical trial too. Start dose of sorafenib was in all case 800 mg: 44.6% could be treated with full dose, 40% needed dose reduction (400 mg) and in 15.3% sorafenib was stopped completely because of adverse event. The most common adverse events were diarrhea (33.3%), fatigue (26.6%), HFS (18%). Best responses are: SD 63.3%, PR 1.4%, PD 32.9%. PFS in patients treated with sorafenib (n=103) was 8.3 month. Mean OS was 13 month. In 29.5% of the cases the serum AFP level was not elevated during treatment. The mean OS for patients with initially normal AFP level and for those with decreasing AFP during therapy was 25 months, while patients having initially elevated AFP levels had a worse prognosis (OS: 8.8 month).

Conclusions: Etiology differs in men and women. The high incidence of diabetes and hypertension suggests, that steatohepatitis is probably more frequent than above. Screening needs to be improved, as only half of hepatitis patients were diagnosed during follow up. The frequency and severity of the adverse events during sorafenib treatment were in accordence with literature data. The level of serum AFP correlated with OS data.

SAFETY AND EFFICACY OF FOLFIRINOX IN PANCREATIC CANCER. A SINGLE CENTER EXPERIANCE.

27

Gábor Lakatos[1], György Bodoky[1]

[1] ***Oncology, St. Laszko Hospital, Budapest, Hungary***

Background: Pancreatic cancer (PC) is one of the most aggressive types of human malignancies and to present it remains a major health problem. Data suggest that the onco-epidemiological situation related to PC in Central European countries is even worse compared to that in the Western world. The management of PC remains a big challenge. The use of the FOLFIRINOX regimen has recently shown survival benefit compared to gemcitabine.

Aim: to evaluate the efficacy and safety of the FOLFIRINOX regimen in PC patients from a single institution.

Patients and methods: data from PC patients receiving FOLFIRINOX chemotherapy at the Department of Oncology of St. László Hospital between January 2014 and April 2016 have been collected. A 20% dose reduction of oxaliplatin and irinotecan was applied from the beginnig of the therapy. Demographic data, data on chemotherapy, adverse events, response to therapy and survival were assessed prospectively.

Results: 38 patients treated with Folfirinox (mean age: 60.5 years, min: 40 years, max: 77 years, males vs. females: 50.0% vs. 50.0%) have been enrolled into the analysis. Patients had performance status (ECOG) scores of 0 and 1 (63% vs. 37%). Most patients had locally advanced cancer (81.6%), only 18.4% had metastatic disease. Folfirinox was used as first line treatment in 87% of the cases, while in 13% of the cases prior gemcitabine therapy was administered. Best response to therapy was stable disease (SD) in 15 cases (43 %), while rapid disease pogression occured in 13 patents (37%). Partial regression (PR) was seen in 7 cases (20%), however only 2 patients underwent surgery with curative intent. After six month of the beginning of Folfirinox 11 patients (36%) had SD or PR.

Nausea (63.1%) and fatigue (71%) were noted as the most frequent adverse events (with grade 3 or 4 severity grades of 18.4% and 13.1%). Alopecia occured in 39.5% of the patients. Severe (grade 3 or 4) neutropenia was observed in 28.9% of the cases, treatment was discontinued for toxicity in 7 patients (18.4%).

Conclusion: FOLFIRINOX is an important therapeutic option in PC for younger patients with good performance status. Stable disease or partial regression could have been achieved in almost two-thirds of our cases, with a considerable number of patients showing no progression after six month of therapy. However, our data do not support the use of FOLFIRINOX as an approach to enhance resectability. The frequency and severity of the adverse events were in accordence with literature data.

SALVAGE THERAPY FOR GERM CELL CANCER

28

Zrna Antunac Golubić[1], Milena Gnjidić[1], Iva Zubatović Đunđenac[1], Marija Gamulin[1]

[1] ***Oncology, University Hospital Centre Zagreb, Zagreb, Croatia***

Intruduction: Germ cell tumours (GCT) account for 2% percent of male neoplasma but are the most common cancer of young men. More then 90% of patients, including those with metastatic disease can be cured with surgery, chemotherapy and radiotherapy. Long term disease free survival cannot be achieved in 5-10 % of patients and optimal salvage therapy for these patients is still unknown. We present outcomes of 27 patients with GCT treated with paclitaxel/gemcitabin (PG) and/or gemcitabine/oxaliplatin (GEMOX) combination therapy in our institution from May 2003 till February 2016.

Materials and methods: The median age at dignosis of all patients was 28 years (17-50).All patients were initially staged II-III, 4 patients had extragonadal GCT, 2 patients had pure seminomatous hystology. Of 21 patients with stage III disease 14 (67%) were classified as poor risk, 5 (24%) as intermidiate and 2 (9%) as good risk. All patients with testicular cancer had orchiectomy performed, followed by cisplatin based chemotherapy and retroperitoneal lymphadenectomy (RPLND) when indicated by our multidsciplinary board. Patients with extragonadal disease received cisplatin based chemotherapy and RPLND. Median time to relapse from diagnosis was 9 months (6-202). 2 patients received high dose chemotherapy with peripheral blood stem cell transplant.

Results: Of 27 patients 25 patients received PG chemotherapy in second or subsequent line, 2 patients received GEMOX and 5 patients received both chemotherapy regimens. Median PFS for PG was 4 months (0-22) and for GEMOX 5 months (0-11). Median OS (defined as time from salvage therapy till death or lost to follow-up) was 14 months. Four patients treated with salvage therapy are still alive, two of them who recieved PG are continuosly disease free.Ten partial responses and one complete response on PG were observed. Median PFS for poor, intermediate and good risk group treated with PG was 2, 2 and 6 months and OS was 11, 37 and 16 months.

Conclusion: Our results show that PG and GEMOX are good options as slavage therapy in previously pretreated patients with metastatic GCT. Large prospective studies are needed to define the best treatment option for patients with poor prognosis.

T790M MUTATION RATE AT THE TIME OF PROGRESSION ON TREATMENT WITH EGFR TYROSIN KINASE INHIBITORS (TKIS) - 2 YEARS OF SINGLE INSTITUTION EXPERIENCE

29

Katja Mohorcic[1], Izidor Kern[2], Urska Janzic[1], Mitja Rot[2], Tanja Cufer[1]

[1] Medical Oncology Unit, University Hospital Golnik, Golnik, Slovenia

[2] Pathology Department, University Hospital Golnik, Golnik, Slovenia

Background: Cell free circulating plasma DNA (cfDNA) EGFR mutation (EGFRmu) analysis could be used to detect resistant mutations and to overcome inconvenience of tissue re-biopsy at the time of progression on first-line EGFR TKIs. Approx. 60% of resistance is supposed to be due to acquired EGFR mutation, namely T790M mutation.

The aim of our analysis was to evaluate the frequency of T790M mutation in cfDNA and in the re-biopsy specimens of advanced EGFRmu-positive NSCLC pts progressing on standard therapy with first-line EGFR TKIs.

Methods: CfDNA EGFRmu determination is a routine clinical practice at our hospital since May 2014. 36 advanced EGFRmu positive NSCLC pts were treated with first-line EGFR TKI since then and followed up at our clinic. Blood samples for EGFRmu analysis were taken at each scheduled visit. Tissue re-biopsy was also performed at disease progression when it was feasible for the patient. Cobas EGFR Mutation Test v1 and v2 (Roche, USA) was used to detect 42 mutations at EGFR gene in exons 18 to 21.

Results: 19/36 pts experienced disease progression according to RECIST 1.1 criteria during the observation period. In all 19 pts activating EGFRmu were re-detected in the blood at the time of progression. In addition, in 9/19 (47.4%) pts also T790M mutation was detected in cfDNA. In 4 out of 10 pts progressing, where only activating mutations were present in cfDNA, tissue re-biopsy was also performed at progression. Tissue re-biopsy increased the detection rate of T790M as de novo detection of T790 in re-biopsy specimen occurred in 3 out of 4 pts.

Overall, T790M mutations in cfDNA and/or re-biopsy was detected in 12/19 (63.2%) of all our pts progressing on first-lineEGFR TKI.

Conclusions: EGFRmu (activaiting or activating + T790M mutations) were confirmed in cfDNA at the time of progression in all our pts with advanced NSCLC treated in everyday clinical practice with non-mutant selective EGFR TKI. The detection rate of T790M mutation in cfDNA was lower than expected, i.e. 47.4%; however, tissue rebiopsy increased the T790M detection rate to 63.2%. Based on our limited series of pts, tissue rebiopsy should be performed, when feasible, in patient without T790M in cfDNA at the time of disease progression on EGFR TKI since further therapeutic options with mutant selective EGFR TKIs are available.

THERAPY OPTIONS FOR STAGE IIIA–N2 NON-SMALL CELL LUNG CANCER PATIENTS

30

Lela Bitar[1], Ivona Markelić[1], Fran Seiwerth[1], Mihovil Roglić[1], Branka Čučević[1], Sanja Pleština[1], Marta Koršić[1], Sonja Badovinac[1], Miroslav Samaržija[1], Marko Jakopović[1]

[1] ***Department for respiratory diseases Jordanovac, University hospital center Zagreb, Zagreb, Croatia***

Introduction: Based on the latest guidelines set by the NCCN for non-small cell lung cancer (NSCLC) management, there are many different therapy options for stage IIIA-N2 disease, which is why we decided to evaluate different therapy options.

Materials and Methods: The medical records of the patients diagnosed with lung cancer in Clinical hospital center Zagreb, Department for respiratory diseases Jordanovac during the year 2012 and 2013 were retrospectively collected and reviewed. Median overall survival (mOS) was measured and analyzed using the Kaplan-Meier and log-rank test.

Results: There were 147 patients diagnosed with stage IIIA–N2 NSCLC, with median age 63 (40-102). There were 105 male patients (71.4%) and 42 female patients (28.6%). Most of them were ex-smokers (54.4%), while only 9.5% never smoked cigarettes. Most of them had very good performance status (ECOG 0-1 91.9%). 78 (53.1%) of the patients were diagnosed with adenocarcinoma, 62 (42.2%) with planocellular carcinoma, 6 (4.1%) with NSCLC-NOS and only 1 (0.7%) with adenosquamous carcinoma. mOS for all diagnosed lung cancer patients was 9 months and for NSCLC it was 8 months. mOS for IIIA-N2 NSCLC was 14 months. Our patients were treated with chemotherapy in 40.8% of the cases (mOS 11 months); sequential chemotherapy and irradiation in 25.2% (mOS 17 months); surgery, sequential chemotherapy and irradiation in 14.3% (mOS 26 months); surgery and adjuvant chemotherapy in 4.1% (mOS 15 months) and neoadjuvant chemotherapy and surgery in 1.4% (mOS 34 months) of the cases, while also 1.4% of all patients were treated with only surgical resection (mOS 4 months); (p=0.001).

Conclusion: We analyzed the data from our Department to assess the difference in management of IIIA–N2 stage NSCLC and the difference in mOS between different therapy options. The majority of our patients were treated with platinum-based doublets only, followed by sequential chemotherapy and irradiation as a second most frequent therapy option. Only 21.8% of the patients were treated with surgery only or combined with other forms of treatment. Only 1 patient underwent concurrent chemoradiation. The difference in overall survival between different therapy options showed highest mOS in patients treated with neoadjuvant chemotherapy and surgery followed by surgery and sequential chemotherapy and irradiation. Sequential chemotherapy and irradiation was superior to chemotherapy. The limitation of our study was a small number of patients in this specific subgroup, so other larger studies should be performed to find difference in mOS between different therapy options for stage IIIA–N2 NSCLC.

THE PROGNOSTIC VALUE OF INTRATUMORAL EXPRESSION OF IL-17A+CD4+, CD4+ AND CD8+ T CELLS IN NON-SMALL CELL LUNG CANCER

31

Jurgita Jackute[1], Marius Zemaitis[1], Darius Pranys[2], Brigita Sitkauskiene[1], Skaidrius Miliauskas[1], Simona Vaitkiene[1], Raimundas Sakalauskas[1]

[1] *Department of Pulmonology and Immunology, Lithuanian University of Health Sciences, Kaunas, Lithuania*

[2] *Department of Pathology, Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania*

Introduction: Immune responses within the tumor microenvironment are increasingly implicated as determining factor in tumor progression and aggressiveness. Different subsets of tumor infiltrating T lymphocytes are believed to play essential role in the immune response to cancer cells.

Study aim was to investigate T cells (IL-17A+CD4+, CD4+ and CD8+) distribution in NSCLC and to determine the prognostic significance of these cells in NSCLC patients.

Methods: We analyzed lung tissue specimens from 80 newly diagnosed and untreated patients who underwent surgery for NSCLC (stages I–III), and 16 control group subjects, who underwent surgery due to recurrent spontaneous pneumothorax. Slides were immunohistochemically analyzed for the expression of IL-17A+CD4+, CD4+ and CD8+ T cells. Quantitative evaluation of these cells was done in 10 most representative high-power fields (HPFs ×400 magnification) per tissue section. The number of cells with positive staining was counted manually in two locations: tumor stroma and tumor islets.

Results: Greater amount of IL-17A+CD4+, CD4+ and CD8+ T cells was found in NSCLC tumor tissue comparing with control group patients (24 [12-47] vs. 4 [2-6], respectively P<0.001; 153 [53-348] vs. 26.5 [18-37] P<0.001 and 166.5 [57-307] vs. 60 [39-115], P<0.001). Predominant infiltration of IL-17A+CD4+, CD4+ and CD8+ T cells was found in tumor stroma compared to tumor islets (P<0.001). Based on univariate stage, pT status, lymph node status, CD4+/CD8+ ratio, total number of tumor infiltrating IL-17A+CD4+ were predictors for OS. A multivariate analysis revealed that total number of tumor infiltrating IL-17A+CD4+ was an independent prognostic factor of reduced survival (HR (95%CI) = 0.31 (0.13-0.77); P < 0.05).

Conclusions: Our study demonstrated that increased total number of tumor infiltrating IL-17A+CD4+ is associated with reduced NSCLC patients' survival.

TREATMENT OUTCOME OF CHILDREN WITH HEPATOBLASTOMA

32

Josip Konja[1], Mirna Aničić[2]

[1] Hematology-oncology, Medical Faculty, Zagreb, Croatia

[2] Pediatric, Klinical Hostiral Centre Zagreb, Zagreb, Croatia

Department of Hematology and Oncology, University Department of Pediatrics, Clinical Hospital Centre Zagreb, University of Medicine Zagreb, Croatia

Background: Hepatoblastoma is the most common malignant primary tumor of the liver in children. The prognosis of hepatoblastoma in children has significantly improved over the last 20 years. This is attributable to improved multidisciplinary input including specialist pediatric hematology-oncology and surgery.

Purpose: To describe the experience in the management of children with hepatoblastoma in Croatia, staged and treated at a single institution.

Patients and Methods: Files of children treated at our hospital between 1995 – 2015 with the diagnosis of hepatoblastoma were reviewed for clinical characteristics and treatment results. All patients presented a palpable abdominal mass. Ultrasound, CT and/or MRI were used to assess site and resectability of tumors. All patients underwent diagnostic biopsy. 11 children (7 male and 4 female, median age at diagnosis was 2.4/ 1-3.5 y) with hepatoblastoma (3 had lung metastases) have been treated according to SIOPEL protocol with pre-operative chemotherapy, surgery and post-operative chemotherapy. One was treated only with chemotherapy (surgery wasn't possible).

Results: The remission has been achieved in all patient; 3 patients died in relapse,1 in remission. 7 patients are still alive in the first remission (also 3 with lung metastases and 1 treated only with chemotherapy). Serious side effects were not noticed (only 1 cardiomyopathy). Secondary malignancies did not occur in any of patients.

Conclusion: Combined modality therapy is optimal treatment for the majority of children with hepatoblastoma. New treatment strategies using innovative approaches are still needed to further improve treatment results.

USE OF COMPLEMENTARY ALTERNATIVE MEDICINE AMONG EARLY BREAST CANCER PATIENTS

33

Eduard Vrdoljak[1], Lidija Boskovic[1], Zeljko Soldic[2], Ingrid Belac Lovasic[3], Branka Petric Mise[1], Marijana Jazvic[2], Nina Dabelic[2], Ljubica Vazdar[2], Dubravka Ledina[1], Maja Bozic Sakic[1], Robert Zorica[2], Marija Petkovic[3], Marija Ban[1], Maja Gasparic[5], Damir Gugic[4]

[1] Clinic for Oncology and radiotherapy, University Hospital Center Split, Split, Croatia

[2] Department of Oncology and Nuclear Medicine, University Hospital Center Sestre Milosrdnice, Zagreb, Croatia

[3] Clinic for Oncology and Radiotherapy, University Hospital Center Rijeka, Rijeka, Croatia

[4] Clinic for Oncology and Radiotherapy, University Hospital Osijek, Osijek, Croatia

[5] Medical Affairs, PLIVA Croatia Ltd., Zagreb, Croatia

Background: This analysis was undertaken to evaluate the extent of use of complementary alternative medicine (CAM) among early breast cancer patients on adjuvant endocrine treatment in Croatia, and to compare sociodemographic and medical characteristics of users and non-users of CAM.

Material and methods: Patients with hormone dependent breast cancer receiving non-steroidal aromatase inhibitors (anastrozole or letrozole) in adjuvant setting (438) were enrolled in this prospective non-interventional study. Both newly diagnosed patients and those already receiving non-steroidal aromatase inhibitors for up to 3.5 years were included. A total of 382 patients (87.2%) answered the questionnaire on use of CAM.

Results: A total of 73 (19.9%) patients reported that they use alternative medicine. Most commonly used forms of alternative therapy are herbal preparations and dietary supplements. They were used by 44/73 (60.3%) of patients. The most commonly used herbal preparations and dietary supplements were aloe vera (22.7%), herbal teas (22.7%), royal jelly (11.7%), propolis (11.7%), and beta glucan (9.1%). Beside herbal preparations and dietary supplements patients also reported use of bioenergy (12.3%), yoga (6.8%), meditation (5.5%), acupuncture (1.4%), homeopathy (1.4%), cristalotherapy (1.4%), magnetotherapy (1.4%), reiki (1.4%) and other (1.4%).

A total of 58 patients (79.5%) who used alternative medicine reported that they trust more to the therapy prescribed by their physician; 6 patients (8.2%) equally trust to the prescribed treatment and alternative therapy, none trust more to the alternative therapy, and 9 patients (12.3%) did not answer this question. There were no statistically significant differences in use of alternative therapy with regards to age, education, employment, income and life standard. There was statistically significant difference in use of alternative therapy depending on previous adjuvant chemotherapy. Patients who received adjuvant chemotherapy used alternative therapy more than patients who did not receive adjuvant chemotherapy (24.4% vs.13.1%; p=0.006).

Conclusion: In comparison with other studies the use of complementary alternative therapy is relatively infrequent among postmenopausal women with early, hormone receptor-positive breast cancer receiving adjuvant endocrine therapy in Croatia. Patients who received adjuvant chemotherapy used alternative therapy more than patients who did not.

Key words:complementary alternative medicine, breast cancer

UTILITY OF INFLAMMATION-BASED PROGNOSTIC SCORING IN PREDICTING OCCURRENCE OF BRAIN METASTASIS IN NON-SMALL CELL LUNG CANCER

34

Marina Serdarević[1], Suzana Kukulj[1], Igor Nikolić[2], Mijo Meter[1], Gordana Drpa[1], Bernard Budimir[1], Filip Popović[1], Miroslav Samaržija[1]

[1] Clinic for Lung disesaes, University Hospital Center Zagreb, Zagreb, Croatia

[2] Department for thoracic surgery, Clinical Hospital Dubrava, Zagreb, Croatia

Background: Recent studies have shown that the presence of systemic inflammation correlates with poor survival in various cancers. In our previously published studies we have shown that higher platelet-to-lymphocyte ratio (PLR) and neutrophil -to-lymphocyte ratio (NLR) values were associated with occurrence of brain metastasis. Additionally, recent studies have shown that CRP and albumin ratio (CRP/Alb ratio) is considered as good prognostic markers for many cancers including lung cancer.

Aims and objectives: The aim of this study was to examine whether CRP/Alb ratio could be a marker to differentiate NSCLC patients with brain metastasis from patients with locally advanced and metastatic NSCLC but without brain metastasis.

Methods: Retrospectively 60 lung cancer patients with brain metastasis at the time of diagnosis and 60 lung cancer without verified or signs of brain metastasis were included in the study. CRP/Alb ratio was defined as the CRP count divided by the albumine count. The CRP and albumine counts of peripheral blood were measured before chemotherapy. Mann-Whitney U test was used to compare the parameters.

Results: No statistically significant difference was determined in CRP and albumin count or CRP/alb ratio between NSCLC patients with brain metastasis and patients with locally advanced and metastatic NSCLC but without brain metastasis.

Conclusion: Although we have previously showed that inflammation based prognostic scores such as PLR and NLR are associated with occurrence of brain metastasis CRP/albumin ratio did not show prognostic value.

WHEN TO PERFORM THE HPV-HR DNA TEST AFTER CONISATION FOR PREINVASIVE DISEASE?

35

Maja Banović[1], Lidija Beketić-Orešković[2], Vesna Mahovlić[3], Kristina Meljanac Salopek[4], Vladimir Banović[1], Ivan Babić[1], Damir Babić[1]

[1] *Department of Obstetrics and Gynecology, University of Zagreb, , School of Medicine, Clinical Hospital Center Zagreb, Zagreb, Croatia*

[2] *Department of Oncology, University of Zagreb School of Medicine, University Hospital for Tumors, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia*

[3] *Department of Pathology and Cytology, University of Zagreb, School of Medicine, Clinical Hospital Center Zagreb,, Zagreb, Croatia*

[4] *Department of Pathology, School of Medicine, University of Zagreb, Zagreb, Croatia*

Background: The incidence of cervical carcinoma has been reduced up to 70% due to the early diagnosis and treatment of the preinvasive disease (CIN, AIS). The optimal surgical procedure for these patients would be a total hysterectomy. However, the population treated are mainly women of reproductive age who still want to give birth. During the follow-up of treated patients according to the current protocol there is a high number of negative patohistological findings at the reoperation, indicated upon the suspicion of residual/recurrent disease. Risks and complications of overtreatment are high and one must take into consideration the psyscholocigal effect on the patient. The implementation of the human papilloma virus DNA testing (HPV DNA test) during the follow-up has been proposed but without the exact protocol.

Aims: We performed this study in order to improve diagnostic accuracy of the follow-up protocol after a treatment for preinvasive cervical disease, at the same time reducing the number of overtreated patients.

Patients and methods: One hundred and fourteen patients were followed up after conisation for CIN3 and/or AIS at 3-6 month, 9-12 month and 18-24 month intervals, then yearly. The follow-up consisted of cytology, colposcopy with biopsy if needed and HPV testing. The end-point of the study was a secondary treatment due to a high suspicion of residual/recurrent disease or disease free period of at least 24 months.

Results: The median follow-up time was 41 months (5-72 months). In predicting residual/recurrent disease cytology had a specificity of 88.9%, sensitivity of 100%, PPV of 33.3% and a NPV of 100% whereas HPV had a specificity of 76.9%, sensitivity of 100%, PPV of 21.4% and a NPV of 100%.

Conclusion: According to our results, both tests cytology and HPV DNA test can be used as a primary follow-up tool after conisation. The choice should depend on a socio-economic aspect. In our setting the HPV test should be done only in those patients with a positive cytology smear any time during follow-up as the point of decision for a second treatment. With this approach we could considerably decrease the number of reoperated patients and co-morbidities.

Key words: human papillomavirus, preinvasive cervical disease, postconisation, HPV DNA test, f ollow-up

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