between both arms, 37 out of 42 patients (88.1%) in the combination treatment group and 46 out of 53 patients (86.8%) in the systemic treatment group. Salvage treatment consisted of systemic treatment in 21 patients (50%) in the combined treatment group, compared to 44 patients (83%) in the systemic treatment group ($p < 0.001$).
Interpretation: This is the first randomized study on the efficacy of RFA. The study met the primary end point on 30-months OS, however the results in the control arm were in the same range. RFA plus systemic treatment resulted in significant benefit on PFS. The ultimate phase II study design does not allow definite conclusions on the benefit or the absence of a benefit of RFA.

6012 POSTER DISCUSSION

Improved Oncological Outcome After Modified Extralevator Abdominoperineal Excision in Low Rectal Cancer Patients

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Background: Introduction of TME surgery has significantly improved the treatment of rectal cancer patients. However, in patients requiring abdominoperineal excision (APE) irradical resections and tumour perforations are still frequent. This study describes an improved oncological outcome when APE was modified to a supine extralevator technique with perineal dissection (sPPD) first.
Material and Methods: From 2000 to 2010, 246 consecutive patients with T3-T4 rectal cancer who underwent an APE were included. All patients were staged with preoperative MRI and received neoadjuvant (chemo) radiotherapy. In 2005 the sPPD approach was implemented as a didactical principle. To avoid false routes and coning in, pelvic dissection must be limited when following the TME planes from the abdomen.
Results: The percentage of irradical resections was 10% for the entire group. After the introduction of perineal dissection first, involved margins were found in 2.2% and 5.7% for cT0−3 and cT4 tumours compared to 6.8% and 30.2% before 2005 ($p = 0.001$). Furthermore, all outcome parameters improved. Local recurrence rate for pre-operativeT4 tumours (cT4) was reduced from 25% to 2.4% and from 34% to 5.6% in pathologic T4 tumours (ypT4). This results in a 3-year local recurrence rate of 1.7% after 2005 versus 11.5% before 2005 ($p = 0.021$). The three year overall survival for the advanced tumours that responded to neoadjuvant treatment (ypT0−3) improved from 83% to 92% as opposed to 52% to 67% in cT4 tumours with no downstaging (ypT4). In a multivariate analysis, perineal dissection first (sPPD) became a significant factor for R1 resection ($p = 0.038$).
Conclusions: The goal in rectal cancer surgery is to obtain negative resection margins. A combination of the appropriate preoperative treatment and improved surgical technique such as sPPD can achieve this goal. From our data it can be concluded that an irradical resection rate below 5% and subsequent local recurrence rate of 2 to 3% should be achievable. In the future it should be unacceptable that suboptimal quality of surgery influences oncological outcome.

6013 POSTER DISCUSSION

Cumulative Exposure to Bevacizumab (BV) After Progression Correlates With Increased Survival in Patients (pts) With Metastatic Colorectal Cancer (mCRC): a Time-dependent Analysis of the ARIES Observational Cohort Study

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Background: BV + chemotherapy (CT) prolongs survival in 1st- or 2nd-line treatment (tx) of mCRC. Prior analyses from ARIES showed that mCRC pts receiving CT/biologics + ⩾1 BV dose within 2 months after 1st progressive disease (PD) had longer post-progression survival (PPS) than pts receiving only CT/biologics. The present analysis evaluated whether cumulative exposure to BV after PD correlates with PPS, with an emphasis on incorporating the dynamic time-varying features of tx patterns seen in the "real world".
Methods: ARIES 1st-line BV-treated mCRC pts who survived 1st PD were included for analysis. PPS was defined as the time from 1st PD to death from any cause. BV exposure, over follow-up, was defined as the cumulative days of BV use from 1st PD. A time-dependent Cox regression model that controls for survival bias towards pts that receive longer exposure to BV was fitted to assess the effect of cumulative BV exposure on PPS, while controlling for potential time-dependent and time-fixed confounders.
Results: As of 2/14/2011, of 1550 enrolled 1st-line pts, 1183 (76.3%) had 1st PD. Characteristics in the 1183 pts were: 56% male, median age of 63 yrs, median ECOG PS of 0, and 76% with colon cancer. The median PPS for all pts with 1st PD was 13.3 months (interquartile range: 5.8, 27.0). Across follow-up, the hazard ratios (HRs) for PPS decreased by an average of 2.1% for each additional 14-day interval of cumulative exposure (range, 1.9–2.3%). Cumulative BV duration was statistically significantly associated with improved PPS ($P < 0.0001$).

Cumulative BV cycles after PD[a]	Follow-up time after PD, days	n(cycles)[b]	n(0)[c]	HR (95% confidence limits)
1	14	191[d]	843[d]	0.977 (0.965–0.988)
2	28	165	766	0.954 (0.932–0.976)
3	42	140	694	0.932 (0.900–0.964)
4	56	120	640	0.910 (0.869–0.953)
5	70	109	607	0.888 (0.839–0.941)
6	84	91	576	0.868 (0.810–0.930)
7	98	84	540	0.847 (0.782–0.919)
8	112	76	514	0.828 (0.755–0.908)
9	126	61	486	0.808 (0.728–0.897)
10	140	49	449	0.789 (0.703–0.886)

[a]A cycle is calculated as 14 days of cumulative exposure after PD.
[b]Pts who received the specified number of post-PD BV cycles by follow-up time.
[c]Pts with no exposure to BV by follow-up time.
[d]Example: At 14 days after PD, 191 pts had a total of 14 days of BV exposure while 843 pts had no exposure to BV.

Conclusions: This analysis suggests that cumulative exposure to BV after PD is associated with corresponding increases in PPS for mCRC pts. Data from a prospective randomized phase III trial testing BV beyond PD are expected soon.

6014 POSTER DISCUSSION

Cetuximab Treatment for Metastatic Colorectal Cancer With KRAS p.G13D Mutation may Improve Progression-free Survival in Japanese Patients

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Background: Anti EGFR inhibitor is recommended for the treatment of metastatic colorectal cancer (mCRC) with KRAS wild type. However, previous study reported that KRAS p.G13D mutation may be associated with a better outcome than the other mutation after treatment with cetuximab. We retrospectively assessed the association between p.G13D mutation and outcome in mCRC.
Material and Methods: We collected records of 98 patients with mCRC genotyped KRAS mutation treated between August 2004 and January 2011 from four hospitals located in Tokyo and Kyushu Island, and reviewed subtypes of KRAS mutation and patient's characteristics. In the patients treated with cetuximab, univariate and multivariate analysis for progression-free survival (PFS) and overall survival (OS) were performed to determine the contribution of KRAS p.G13D mutation.
Results: The frequency of KRAS p.G13D mutated tumour was 23 (23.5%) and the other mutated tumour was 75 (76.5%). Of the 98 patients, 31 were treated with cetuximab; KRAS p.G13D mutation were 9 (29.0%) and the other mutation were 22 (71.0%), respectively. There were no significant differences in age, sex, primary site, pathological type, previous chemotherapy history and irinotecan combination. The univariate analysis for PFS and OS did not show significant difference between the KRAS p.G13D mutation and the other mutations (PFS; median 4.5 months vs. 2.8 months, $p = 0.65$, OS; median 15.3 months vs. 8.9 months, $p = 0.51$). However, the multivariate analysis for PFS showed a trend that

favored p.G13D mutation (PFS; HR = 0.29; 95% CI, 0.08–1.10; p = 0.07, OS; HR = 0.23; 95% CI, 0.04–1.54; p = 0.13) (Table).
Conclusions: These results suggest that the use of cetuximab may be associated with improvement of PFS among patients with mCRC who have KRAS p.G13D mutated tumours compared with the other mutated tumours. Further study is needed to clarify the benefit of cetuximab treatment for KRAS p.G13D mutated tumours in mCRC.

Table: Multivariate analysis for PFS and OS in the patients treated with cetuximab

	Total		PFS				OS			
KRAS type	No	%	Median	HR	95% CI	*p*	Median	HR	95% CI	*p*
p.G13D mutation	9	29.0	4.5 m	0.29	0.08–1.10	*0.07*	15.3 m	0.23	0.04–1.54	0.13
Other mutations	22	71.0	2.8 m	1	referent		8.9 m	1	referent	

6015 POSTER DISCUSSION

An International Consortium in Chemo-refractory Metastatic Colorectal Cancer Patients Shows Cetuximab Efficacy in Patients Harboring HER2 Gene Copy Number Gain

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Background: KRAS mutation represents the only validated biomarker used in clinical practice for selection of metastatic colorectal cancer (mCRC) candidate for a therapy with the anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibody cetuximab. Previous studies, conducted in small cohorts of patients suggested that HER2, the major EGFR partner, could modify the sensitivity to anti-EGFR agents. Aim of the present study was to investigated the role of HER2 gene copy number in a cohort of mCRC patients treated with cetuximab.
Materials and Methods: Chemorefractory mCRC patients treated with cetuximab alone or in combination with irinotecan were collected in an international consortium effort. Her2 gene status was analyzed using the dual color FISH assay LSI HER2/neu-CEP17 (PATHVYSION, Abbott) in one central lab, whereas K-Ras and BRAF mutations were investigated locally. Logrank and Chi-square tests were applied at statistical level.
Results: Four hundred and seven patients were collected. Objective response rate (ORR) was observed in 25.3% of patients. HER2 gene status was evaluable in 288 (70.8%) cases. Two different scores were applied for HER2 gene status evaluation: the Colorado (positive vs negative cases, where positive are $\geqslant$ 4 copies of the gene in $\geqslant$ 40% of cells or gene amplification) and the Locarno score (based on the classical cytogenetic criteria, positive case are those with at least low polysomy). With the Colorado score, positive cases (81 cases, 28.8%) experienced response in 34.6% of patients (vs 15.7% in negative cases, P < 0.001), with an overall median progression free survival (PFS) of 5.14 months (vs 3.0 months in negative cases, P = 0.004) and a median overall survival (OS) of 10.9 months (vs 9.8 months in negative cases, P = 0.44). With the Locarno score, positive cases (81 patients) showed an ORR in 30.3% of patients (vs 11.4% in negative cases, P = 0.027), with a median PFS of 4.1 months (vs 1.8 months in negative cases, P = 0.002) and a median OS of 11.3 months (vs 7.8 months in negative cases, P = 0.2). By stratifying cases with KRAS and BRAF mutations, no significant differences in terms of ORR, PFS and OS were observed between HER2-positive and negative cases using both scores, although similar trends were found.
Conclusions: Data from this large retrospective study suggested that HER2 gene status by FISH may represents an additional marker useful for the identification of mCRC patients who might benefit from EGFR-targeted therapies. The interplay between EGFR and HER2 needs to be more deeply investigated for future best tailored treatments.

6016 POSTER DISCUSSION

Prognostic and Predictive Value of Mucinous Adenocarcinomas in Colorectal Cancer Patients Treated With Chemotherapy and Targeted Therapy

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Background: Mucinous adenocarcinomas (MC) have a different clinical behaviour compared to the more common histological subtypes of colorectal cancer (CRC). The aim of this study was to investigate the prognostic and predictive value of mucinous histology in advanced CRC patients treated with first-line systemic treatment.
Material and Methods: The study population included 552 and 547 advanced CRC patients who participated in the CAIRO and CAIRO2 study, respectively. Patients were classified according to the histology of the primary tumour, and only patients with a MC (n = 99) or adenocarcinoma (AC)(n = 911) were included in our analysis.
Results: In the CAIRO and CAIRO2 study, MC were present in 50 and 49 patients, and AC in 435 and 476 patients, respectively. In both studies, patients with MC had more often a lower serum LDH at baseline (p < 0.01), extrahepatic localization of metastases (p < 0.01), a larger diameter (p < 0.02) and microsatellite instability (MSI) of the primary tumour (p < 0.01) compared to patients with AC. In the CAIRO study, T stage (p = 0.02) of the primary tumour and the number of involved metastatic sites (p = 0.05) were higher in patients with MC. In the CAIRO2 study, the median age at randomisation (p = 0.01) was higher and *BRAF* mutations (p = 0.002) were more frequently observed in patients with mucinous histology compared to patients with AC.
In the CAIRO and CAIRO2 study, the median overall survival (OS) was significantly reduced for patients with MC compared to patients with AC (13.2 vs. 19.2 months; p = 0.03; 13.1 vs. 21.5 months; p = 0.009). In multivariate analysis, mucinous histology remained a strong predictor for OS in both studies. Additionally, the CAIRO2 study showed also a decreased progression free survival (PFS) in patients with MC compared to AC (7.2 vs. 10.6 months; p < 0.0001). In both studies, the overall response rates for patients with MC were significantly worse and they received less cycles of systemic treatment compared to AC patients. The reasons for discontinuation of study treatment were not significantly different between patients with MC and AC. There was no difference in the incidence of grade 3 or 4 adverse events between both patient groups.
Conclusions: This large retrospective analysis showed that patients with advanced mucinous CRC have an unfavourable OS and worse response to first-line fluoropyrimidine based chemotherapy in combination with targeted agents. The mechanisms for treatment resistance should be further investigated.

6017 POSTER DISCUSSION

Quality of Life and Reintegration of Long-Term Survivors of Colorectal Cancer: a Population-Based Study

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Background: The number of long term colorectal cancers is increasing. Cancer and its treatment can cause physical and psychological complications, but little is known about how it impacts on quality of life (QOL) and on reintegration in the long-term 5, 10 and 15 years after diagnosis.
Material and Methods: Cancer survivors were randomly selected from three tumour registries in France in 1990, 1995, and 2000. Controls were randomly selected from electoral rolls, stratifying on gender, age group, and residence area. Participants completed four standardized questionnaires: MOS SF36, EORTC QLQC30, MFI, STAI, and a life conditions questionnaire. Differences in QOL scores between survivors and controls were evaluated using an analysis of variance. Differences of changes in family, social, and professional life were evaluated as relative risks, using a logistic regression.