231 POSTER

Prospective randomised trial comparing multimodal therapy with surgery alone for oesophageal adenocarcinoma: a long-term follow-up

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Background: A randomized trial showed a survival advantage for neoadjuvant chemoradiotherapy prior to surgery over surgery alone at 3 years followup. The aim of this study was to assess if this survival advantage was durable. We performed long term follow-up on patients randomized to neoadjuvant chemoradiotherapy versus surgery alone and all patients were followed-up for more than 7 years.

Method: Patients were recruited between May 1990 and September 1995 inclusive (n=113). Patients assigned to the multimodal group received two courses of chemotherapy in weeks 1 and 6 (fluorouracil, 15mg per kg for five days and cisplatin, 75mg per kg on day 7) and a course of radiotherapy (40Gy, administered in 15 fractions over a 3 week period beginning concurrently with the first course of chemotherapy), followed by surgery. Long-term follow-up was performed via chart review and family doctor contact. Survival was measured from the date of randomization to the date of death or most recent follow-up. Estimates of median survival are based on the Kaplan-Meier method: group comparisons of survival involving individual variables were based on the log-rank test.

Results

	Multimodal Therapy	Surgery Alone
No. Patients	58	55
Mean survival (Months)	54	19
Median Survival	17	12
Downstaging (% node negative at resection)	55	18
Complete Response (%)	22	0
Median Survival for Complete Responders (months)	67	-
Stage 2a median survival (months)	67	11.5
Survival Node+ (months)	9	15

Discussion: The survival advantage conferred by neoadjuvant chemoradiotherapy is durable with a significant difference maintained at 7 years allaying fears that the benefit seen at three years is transient.

232 POSTER

Evaluation of messenger RNA of Beta-1,6-N-acetylglucosaminyltransferase V as a molecular marker for micrometastasis in gastrointestinal cancer.

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Background: Deregulated glycosylation patterns are characteristic of metastatic phenotype. Malignant transformation is accompanied by increased beta-1,6-GlcNAc branching of N-glycans attached to Asn-X-Ser/Thr sequences in mature glycoproteins. Beta-1,6-N-acetylglucosaminyltransferase V (GNTV) catalyzes the addition of beta-1,6-GlcNAc to N-glycan on glycoproteins. GNTV functions seem to be involved in focal adhesion turnover and signaling through PI3K/Akt.The amount of GNT-V correlates with disease progression.

Aims: In order to detect micrometastasis (MM) in patients with gastrointestinal cancer (GC) we have developed a model system based on reverse transcriptase (RT)-PCR amplification of GNTV mRNA.

Methods: As a surrogate model to asses sensitivity, GNTV mRNA expression was analyzed in a panel of 9 human GC cell-lines (CL), including 2 CL developed in our laboratory: pancreatic carcinoma MBQ-OJC1 and colon carcinoma JJPF-OJC4. The specificity of GNTV mRNA was examined by PCR amplification of cDNA from normal lymph nodes (LN), bone marrows (BM) and peripheral blood (PB, cellular and plasmatic mRNA).

Results: Specific amplicon for GNTV was demonstrated by RT-PCR in all the GCCL tested. Using a hot-start PCR and defined amounts of input RNA, GNTV transcripts were not detected in normal LN (pooled, n=34) and BM (pooled, n=83). GNTV mRNA expression in PB was detected on 1 among 14 healthy donors analyzed.

Conclusions: We have developed a model system based on RT-PCR for GNTV mRNA in order to detect isolated and circulating micrometastatic cells in patients with gastrointestinal cancer. GNTV could serve as a sensitive and specific molecular marker for targeting micrometastasis in PB, LN and BM. Support: Xunta de Galicia PGIDT01PXI90001PR.

233 POSTER

Thymidylate synthase is a predictor for response and survival of patients with isolated unresectable liver tumors receiving hepatic artery infusion chemotherapy

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Introduction: Fluoropyrimidine (FP)-based hepatic artery infusion (HAI) chemotherapy is one promising approach when a primary or secondary liver tumor cannot be resected surgically. Thymidylate synthase (TS) is a key enzyme for DNA synthesis and targeted by FPs. Several studies have shown that high TS levels are associated with resistance to systemic 5-fluorouracil (5-FU) based chemotherapy. The aim of this study was to investigate the influence of TS mRNA levels on response and survival of patients receiving FP-based HAI.

Patients and methods: Fifty-one consecutive patients with liver tumors receiving HAI with available tumor tissue for TS quantitation were entered between 1991 and 2001 into this study. Fourty-one patients suffered from colorectal cancer, 4 from primary liver cancers, and 6 from other cancers. Patients (29 men and 22 women) had unresectable metastases limited to the liver or primary liver tumors with a mean age of 58 years (range: 28 to 76 years). Tumor tissue was obtained at laparotomy for the intra-arterial infusion device implanation. Relative TS mRNA quantitation was performed by RT-PCR using beta-actin as internal standard.

Results: Median TS expression was 2.2 with high variation between tumors ranging from 0.1 to 27. Twenty-two out of 51 patients responded to HAI (CR + PR). The median TS level of the responders was 1.6 and more than two-fold lower than the level of the non-responders (n = 29) with 3.3. In the subgroup with TS $\leq$ 3.0 18 out of 29 patients responded, whereas in the subgroup with TS > 3.0 only 4 out of 22 responded (p = 0.04). Moreover, all patients with very high TS > 4.5 (n = 13) did not respond (NC or PD). The median survival from start of HAI for all patients was 18 months (range: 3 to 97). Patients with TS levels $\leq$ 3.0 showed with 24 months a longer median survival duration compared to patients with TS levels > 3.0 wit 15 months (p = 0.016).

Conclusion: Patients with lower TS levels showed a better response rate and had a longer survival duration compared to patients with higher TS levels. Thus, TS levels also seem to influence the prognosis of patients receiving FP-based HAI. Additionally, patients with very high TS levels do not seem to profit from FP-based HAI.

234 POSTER

Immunohistochemical characterization of human hepatocellular carcinomas

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Background: It has been known for a long time, that alfafetoprotein (AFP), an oncofetal marker is expressed in approximately half of hepatocellular carcinomas (HCC). However its production is not perceived to be related with the clinical behaviour of the tumors. Recently two independent microarray studies described different expression profiles for AFP positive and negative HCC cell lines (Hepatology 2001, 33, 676, Hepatology 2002, 35, 1134). We decided to compare immunohistochemical characteristics of AFP positive and negative clinical HCC samples.

Material and methods: Immunohistochemical staining for different antigens (AFP, β-catenin, P53, CD44, MSH-2, MLH-1) were done on 31 paraffin embedded tumor samples. The results were compared with the most important clinical parameters.

Results: Sixteen tumors was AFP positive. Gender and age of the patients, etiological factors, histological type of the tumors, MSH-2, MLH-1 expression did not segregate between the AFP positive and negative tumors.