1237 PUBLICATION

Surgical treatment of lymph node metastases of papillary thyroid carcinoma – Possible prognostic value

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Purpose: Lymph node metastases of PTC are frequent (>70%). Their prognostic importance, as well as value of the extent of surgery are controversial. The aim of this study was to analyse survival rate according to prognostic factors, prognostic value of lymph-node metastases of PTC and possible impact of surgery.

Methods: From January 1981, to January 1997, there was 148 patients surgically treated due to PTC. Total Thyroidectomy (TT) was undertaken in 140 patients – [111 TT + dissection of the central and lower jugular lymph nodes for frozen-section hystopathology; of these 80 (72.1%) patients with metastases in lower jugular lymph nodes, were treated with Modified Radical Neck Dissection (MRND) in the same act]. Palliative and diagnostic surgery of advanced forms PTC in 8 cases. Age: 43.71 ± 15.03 with Median 43 and Rang (7–80). Sex ratio: F/M – 3.1/1. Survival analysis: Kaplan-Meier, Log Rank, Wilcoxon test.

Results: Overall survival rate in this group during the 183 months follow-up reaches 84.15%. We found age over 45 (p-1.21 × 10^{-6}), tumor size over 40 mm (p-0.014), as well as extracapsular involvement (p-0.01) and distant metastases (p-4.72 × 10^{-11}), as bad prognostic factors. According to this data we found no significant difference in 15 years survival rate comparing presence or absence of lymph node metastases, either in central or jugulocarotid regions.

Conclusion: Preoperative diagnostic of lymph node metastases of PTC (frozen section) is important for adequate surgery and could have same impact on prognosis.

Pancreatic and gastric cancer

1238 ORAL

Positron emission tomography (PET): Diagnostic benefit in pancreatic tumors?

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Purpose: In patients with tumors of the pancreatic head, distinction between inflammation and malignancy can be tricky since even modern imaging techniques often are contradictive in preoperative evaluation, and since clinical symptoms can be misleading.

Methods: We compared the diagnostic value of preoperative FDG-PET in 159 patients with pancreatic tumors, such as pancreatic malignancies (n = 89), pancreatitis (n = 48) and benign pancreatic tumors (n = 22) with ERCP and CT. After translation of the original reports into a five point malignancy scale (no, probably not, indeterminate/technic. unsuccessful, probable, definite tumor), results were compared using ROC analysis.

Results: The diagnostic values (area under ROC curve) were 0.93 (ERCP), 0.86 (PET), and 0.82 (CT). Most false PET results were associated with elevated fasting glucose levels (false negative) or acute bouts of chronic pancreatitis (false positive). If patients with fasting glucose levels ≥130 mg/dl (n = 16) or ≥3-fold elevated inflammation blood chemistry index (n = 17) were excluded from evaluation, the ROC areas for the remainders (n = 126) were 0.94 (PET), 0.94* (ERCP), and 0.84 (CT). The diagnostic combination revealed 0.98* (ERCP+PET), and 0.94 (ERCP+CT) and 0.94 (PET+CT), respectively (*p < 0.02). Time to surgery was not prolonged by PET procedure. False positive metastases were seen in 9%. Surgically relevant questions, such as local resectability of the tumor or mesenteric/portal vascular infiltration were not answered by PET but by cellacography. PET was in 65% of cases of diagnostic value (additional or diagnosis confirming information), and in 5% misleading, seen retrospectively.

Conclusion: There is a diagnostic benefit of PET in preselected patients and in combination with ERCP, but PET is unlikely to influence the rate of negative laparotomies in unresectable pancreatic tumors.

1239 ORAL

Radiotherapy and 5-FU after curative resection for the cancer of the pancreas and peri-ampullary region: A phase III trial of the EORTC GITCCG

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Purpose: To investigate the survival benefit of radiotherapy (2 × 20 Gy, split course) and 5-FU (Trt) as compared to surgery alone (Obs).

Methods: Eligible patients with T_{1-2} N_{0-1a} M_0 pancreatic head or T_{1-3} N_{0-1a} M_0 peri-ampullary cancer, histologically proven adenocarcinoma and WHO performance status ≤2 were randomized after a curative resection. Patients were stratified by institution and tumor localization.

Results: Between 9/87 and 4/95, 218 patients were randomized, 108 pts on Obs and 110 on Trt and 18 pts were ineligible (10 Obs and 8 Trt). Baseline characteristics were comparable between the two groups. One hundered and nineteen pts (55%) had pancreatic head cancer (61 on Obs and 58 on Trt). In the Trt arm 22 pts (22%) did not receive any treatment because of post-operative complications and patient refusal. Based on the 80 eligible pts for whom the treatment started, 74 received 40 Gy and the median dose of 5-FU was 90% of the maximum theoretical dose. Only minor toxicity was observed. The median duration of survival was 19.1 months on Obs and 23.5 months on Trt (logrank P = 0.216). The two year survival estimates were 42% (95% CI: 32–52%) and 50% (95% CI: 40–60%) on Obs and Trt, respectively. The results were not changed when stratifying for tumor location.

Conclusion: Adjuvant radiotherapy in combination with 5-FU is well tolerated. Nevertheless, this was not accompanied by a clear survival benefit.

1240 ORAL

Activity and tolerability of gemcitabine plus cisplatin in advanced metastatic pancreatic carcinoma

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Purpose: Single-agent GEMZAR® (Gemcitabine HCl) has been shown to produce statistically significant Clinical Benefit, survival and time to disease progression, when compared with 5-FU in a randomized trial in patients (pts) with locally advanced and metastatic pancreatic cancer (Proc Am Soc Clin Oncol 1996, 15, 506, abstr 1624).

Methods: We report the preliminary results of an ongoing study, using the combination of gemcitabine 1000 mg/m^2 given as a 30 min infusion on days 1, 8, 15 of a 28 day schedule, and cisplatin 50 mg/m^2 on days 1 and 15 in chemonaive pts with bidimensionally measurable advanced adenocarcinoma of the exocrine pancreas.

Results: 41 pts (16 F, 25 M; median age 53.9 years) were enrolled. Median Karnofsky performance status was 80% (range 60–100%). 6 pts had locally advanced unresectable tumours with regional nodal metastases: 35 pts had metastatic disease. The median number of cycles administered was 4.2 (range 1–11). Therapy was mostly well tolerated on an outpatient basis. Grade 3 and 4 toxicity was as follows: neutropenia in 19/0% (of cycles), thrombocytopenia in 21/9.7%, haemoglobin 14.6/0%, nausea/vomiting in 12.1/2.4%, alopecia in 2.4/0%. Of 37 evaluable pts (4 pts not evaluable having received <1 cycle) there was 1 CR and 2 PRs (8.1%, 95% CI 15–35%), and 18 pts with stable disease (48.6%). Also, 1 patient had a CR but was lost to follow-up and this CR could not be confirmed. 7 additional pts had tumour reductions but did not have bidimensionally measurable disease and were not evaluable. Responses occurred after 4–6 cycles. Median survival is currently 8.6 months.

Conclusions: The combination of gemcitabine and cisplatin is active and well tolerated in pts with advanced and metastatic pancreas cancer.

1241 ORAL

Microsatellite instability in gastric cancer

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Purpose: The frequency of microsatellite instability (MI) and its association

with clinicopathologic features and prognosis was studied in 126 curatively (R0) resected gastric carcinomas.

Methods: DNA was extracted from 126 formalin-fixed, paraffin-embedded gastric carcinomas and corresponding normal mucosa. Each case were studied with a panel of at least 5 to 10 microsatellites containing mononucleotide and dinucleotide repeats. A tumor was considered as positive when at least one locus showed a different mobility band.

Results: MI could be detected in 44.4% (n = 56) of all tumors. 12.8% (n = 16) of the tumors showed MI in two and more loci. 32 (57.1%) of the 56 MI positive carcinomas belonged to the intestinal type, 21 (37.5%) to the diffuse type and 3 (5.4%) to the mixed type according to the Lauren classification. No significant difference could be demonstrated concerning the mean survival time of MI negative carcinomas (2.92 years) and MI positive carcinomas (2 35 years). MI was not correlated with age, depth of invasion or differentiation. However 5 of 6 (83%) cases demonstrating widespread MI (≥4 loci with MI) were free of lymph node metastasis. In comparison only 36 of 70 (51.4%) MI negative tumors were nodal negative.

Conclusions: MI is not infrequent in gastric cancer but no significant association could be demonstrated between MI and prognosis.

1242 ORAL

Expression of the β4 integrin subunit is closely related to hematogenous metastasis in gastric cancer

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Purpose: Alterations in cell attachment to the extracellular matrix are postulated to play an important role in the process of invasion and metastasis. Laminin distribution patterns have already been shown to influence the mode of spread of gastric CA. Very little is known about the influence of laminin receptors like the α6β4 integrin on the pattern of metastasis of gastric CA.

Methods: We evaluated immunohistochemically the expression of α6β4 in specimens from 48 patients with advanced gastric CA. The relationship between the expression of α6β4 and the clinico-pathological features of the tumors was statistically analyzed.

Results: In 10/48 (21%) tumors, the expression of the β4 subunit was found to be as strong as in the normal mucosa. This was seen predominantly in gland-forming CA ($p < 0.05$), showing a marked expression of laminin ($p < 0.005$) and a low rate of tumor cell dissociation ($p = 0.06$). After a mean follow-up of 19 months, 10 patients had developed hematogenous metastases. 6/10 (60%) presented a strong expression of β4, whereas only 4/38 (11%) patients without hematogenous metastasis showed this expression pattern ($p > 0.01$).

Conclusion: Our findings indicate, that the β4 integrin subunit may play an important role in the process of hematogenous metastasis in gastric CA.

1243 ORAL

Serum tumor markers in gastrointestinal cancer patients: A prospective longitudinal study

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Purpose: The present study was designed to evaluate in a prospective trial, the ability of a combination of CA 72-4, CEA and CA 19-9 tumor markers to improve the clinical diagnosis of recurrent gastrointestinal (GI) cancer.

Methods: 300 GI cancer patients were enrolled. Patients with colorectal cancer, stages A, B C and D (with surgically resectable metastasis), and with gastric cancer, stages I, II, III and IV (only T4N2M0) entered the study. Patients were followed for at least 4 years after surgery or until diagnosis of recurrent disease. Serum samples were obtained before surgery and at every time point scheduled for the clinical follow-up. CA 72-4 and CA 19-9 RIA kits were kindly supplied by Centocor, Malvern, PA. Serum CEA levels were measured using the CEA RIA kit (Abbott).

Results: To determine whether the combined measurement of these tumor markers may be considered an indication to perform imaging diagnostic procedures, all patients whose serum levels of at least one of the three tumor markers became positive or increased more than 50% (over the mean of at least 3 previous determinations), were suspected as having recurrent disease, and therefore, were subjected to detailed imaging procedures. Among the 300 patients, 82 had recurrent disease. In more than 80% of the cases, the serum levels of at least one marker significantly rose, allowing either a confirmation or a prediction of the diagnosis of recurrent disease. No false positive cases were observed.

Conclusion: In all the cases, the serum marker performance matched the diagnostic imaging procedures, suggesting their possible use as a pilot tool to guide imaging diagnostic procedures during the post-surgical follow-up.

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1244 ORAL

Randomised clinical study (phase III) FE vs. FEP in advanced gastric cancer

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Purpose of the study was to determine activity of high doses of 5-fluorouracile and epirubicin (FE) vs. the same combination + cisplatin (FEP) in advanced gastric cancer.

Methods: In prospective phase III clinical study 110 pts. with advanced gastric cancer were included. Out of 110 pts. 100 (69 male, 31 female) were evaluable. The treatment involved in FE arm 1000 mg/m2 in 6 hour-infusion of 5-fluorouracile on days 1, 2, 3, 4, 5 and 120 mg/m2 of epirubicin i.v. on day 1; in FEP arm the same combination of cytostatics + cisplatin 30 mg/m2 on days 2.4 was administered. The cycles were repeated after 4 weeks.

Results: In FE arm 51 patients were evaluable with 1 complete and 14 partial remissions (31.4%), and in FEP arm out of 49 evaluable patients 2 complete and 17 partial remissions (40.8%) were observed.

Median survival in FE group was 6.7 mos, and in FEP group 8.9 mos. The survival difference is statistically significant ($p = 0.1959$). Febrile neutropenia (grade IV) was observed in 3 patients in arm FE and in 5 patients in arm FEP. The treatment related death was not registered.

Conclusion: The addition of cisplatin to high doses of 5-fluorouracile and epirubicin resulted in statistically significant better response to therapy.

1245 ORAL

Taxotere-cisplatin (TC) in advanced gastric carcinoma (AGC): A promising drug combination

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Despite chemotherapy (chemo), the outcome of patients (pts) with AGC remains dismal. Taxotere (TAX) was shown to induce alone an interesting response rate of 24% in AGC. We conducted a phase HI trial investigating its activity in combination with cisplatin.

Pts with AGC not pretreated palliatively by chemo, with measurable disease, PS ≤ 1, normal blood count, and normal hepatic and renal functions received up to 8 cycles of TC (TAX 85 mg/m^2 d1, Cisplatin 75 mg/m^2 d1) q3w. TAX escalation to 100 mg/m^2 in 5 pts was too toxic and discontinued.

Among 41 pts already accrued, 37 pts (mean age 55 y, mean weight 62 Kg, M:F 31:6) are evaluable for toxicity (tox) and 31 for response. We observed 2 CR and 16 PR (RR = 58%, 95%CI: 39–75%). 3 fatalities occurred: 2 pulmonary embolisms and 1 suicide. Grade ≥3 tox were neutropenia 72%, thrombocytopenia 8%, alopecia 30%, fatigue 8% mucositis 5%, neurologic 3% and nausea/vomiting 3%. 4 of 153 cycles were complicated by non-fatal febrile neutropenia, 2 of them with TAX 100 mg/m^2. Other tox were grade 1–2 neurotoxicity 40% and fluid retention 30%, 4 grade 1 renal tox and 2 grade 1 hypersensitivity reactions.

We conclude that TC, as used, is well tolerated with significant efficacy in AGC. The planned accrual of 43 pts is about to be reached and mature results should be available for the conference.

1246 POSTER

Prognostic factors in non-curative gastric cancer

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Objective: To identify the importance of the extent site and distribution of residual intra-abdominal disease in patients having non-curative resection for gastric cancer and so assess the indications for extended resection.

Method: 230 patients who were explored with curative intent but in whom the resection was palliative because of residual microscopic (R1) or residual macroscopic (R2) disease were identified from a prospective data