

Methods: One hundred and three patients entered into the study. The experimental group received preoperative radiation therapy (n = 49), the control group-surgery alone (n = 54).

Results: Similar overall survival was observed in patients of the experimental and the control groups: median survival was 40 and 48 months, 3 year survival rate (YSR) $54 \pm 7\%$ and $54 \pm 8\%$, 5 YSR $46 \pm 8\%$ and $44 \pm 7\%$, 10 YSR $41 \pm 8\%$ and $31 \pm 7\%$ respectively. When various subgroups of patients were analyzed the results showed significant difference. The most impressive advantage of the combined treatment modality was seen when N positive cases were compared: median survival was 37 and 17 months, 3 YSR $50 \pm 11\%$ and $35 \pm 10\%$, 5 YSR $45 \pm 11\%$ and $10 \pm 6\%$, 10 YSR $28 \pm 8\%$ and $10 \pm 6\%$ respectively.

Conclusion: Adjuvant radiation therapy can improve surgical results in selected groups of patients with resectable gastric cancer.

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PUBLICATION

The influence of trypsin, chymotrypsin and papain on the growth of human pancreatic adenocarcinoma transplanted to *nu/nu* mice

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Purpose: The aim of the study as presented was to investigate the influence of protease mixture in a model of transplanted human pancreatic carcinoma based on our previous results in mice syngenic tumor models.

Material and Methods: After the 2 weeks of postransplant latency, total of 18 *nu/nu* mice (CD-1 prone) bearing subcutaneous human pancreatic adenocarcinoma were as random divided into two equal groups. The 1st one (enzyme group) was administered with trypsin, chymotrypsin and papain solution rectally. The 2nd one (control group), was administered with saline by the same way. The tumour growth in both groups was measured daily for following 30 days and the tumor mass was calculated from their extents.

Results: Along the presented study, protease mixture retards growth of human pancreatic adenocarcinoma in *nu/nu* mice. In the enzyme group, the tumor mass increased up only to 47.6% of the control volume in the 30th day.

Conclusion: Although, the proteases were expected to have mainly the antimetastatic effect in cancer progression, these results confirm growth inhibition of primary tumor by trypsin, chymotrypsin and papain solution.

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PUBLICATION

Gemcitabine (G) in combination radiationtherapy (RT) in stage III-IV pancreatic cancer: First results of a current Phase I study

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The purpose of the study was to determine the maximal tolerated dose (MTD) of G. in combination with radiation in patients with stage III/IV pancreatic cancer since it is known that G. is a potent radiation sensitizer of human pancreatic cells in vitro (Int. J. Radiat. Oncol. Biol. Phys. 34: 867, 1996). Also it has been reported, that dose of G. of 500 mg/m² might be a tolerable dose when G. was delivered concurrently to radiation (C.J. Mc Ginn ASCO 1998, Abstr. 1014).

Material and Method: The therapy encompassed a radiation of the primary tumor region and the lymphatic drainage paths up to the hilar region of the liver. A total dosage of 50.4 Gy was targeted based on a single dose per day of 1.8 Gy. The radiation was carried out on all patients on the basis of a continuous course and with a three-field-box technique. The volume of treatment amounted to 1–1.5 liters. G. was applied on days 1, 8, 15, 22 and 29. The radiation therapy followed one hour after the G. application (30 minute iv infusion.). The dose escalation started from 200 mg/m² and increased in 50 mg/m² steps, up to 350 mg/m². At each dose level a cohort of three patients were treated and increased to 6 patients when grade 3/4 hematological and non hematological toxicities appeared, except nausea, vomiting and hair loss.

Results: 16 patients have been entered the study so far. No grade 3/4 toxicity was found at dose level 1 of G. 200 mg/m² and at dose level 2, G 250 mg/m². Because of lack of significant toxicity it has been decided to enroll 2 patients on dose level 2. However, at dose level 3 (300 mg/m²), grade 3 leukopenia was found in 2 out of 6 patients. Beside the hematological toxicity grade 1/2 nausea and vomiting was observed and 1 patient with grade 4 toxicity of ALT and AST.

Efficacy: At dose level of 200 mg/m² one patient was found as stable disease (SD), 2 patients progressed during therapy. 1 patient at this dose level is still alive after 8 month. At dose level 2 (250 mg/m²) one patient progressed and one patient is still alive after completing the therapy. At dose level 3 (300 mg/m²) all patients developed SD. Progression have been seen after 4 month, 3 month and 1 month respectively and 2 patients are still stable disease.

Currently 6 patient are enrolled on dose level 3 (350 mg/m²). At this is dose level 2 patients developed Grade 3 and grade 4 leukopenia.

Conclusion: G. in combination with radiation shows a different MTD when given 1 hour before radiation. The study is still ongoing.

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PUBLICATION

Gastric carcinoma: A phase II study of capecitabine with new dosing regimen in patients with advanced/metastatic gastric carcinoma

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Purpose: Capecitabine is a fluoropyrimidine carbamate with anti-neoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-FU. We investigated efficacy and toxicity of capecitabine in advanced/metastatic gastric carcinoma patients.

Methods: Capecitabine was administered at a daily dose of 1657 mg/m² for 3-weeks followed by a 1-week rest period and given as 4-week cycles. This treatment dosing regimen was determined from its MTD (2510 mg/m²) in continuous dosing of a phase 1 study in Japan. Eligibility criteria were as follows: 1) histologically/cytologically confirmed gastric carcinoma with measurable and/or evaluable lesions, 2) PS 0–2, 3) age <75, 4) prior chemotherapy no more than 1 regimen, 5) adequate bone marrow, liver, renal and cardiac functions, 6) written informed consent.

Results: Totally, Thirty-two patients were entered into a multi-center phase 2 study from July 1996 to December 1997. One patient was ineligible due to prior chemotherapy violation. Patient characteristics in 31 eligible cases were 22 males, 9 females, median age 61 (range 36–74). The number of treatment cycles ranged from 1 to 9. Overall response rate was 19.4% (95%CI 7.5–37.5%) in 31 eligible cases, and the response rate in patients without prior chemotherapy (including no chemotherapy in the adjuvant setting) was 24% (6/25). Only one NCIC CTC grade 3/4 related adverse event, increase in total bilirubin (grade 3, 6.3%) occurred in >5% of patients. Other related grade 3 adverse events were skin rash, increase in GOT, increase in blood sugar, decrease in hemoglobin & hematocrit, and increase in creatinine (each 3.1%). There was no other related grade 4 adverse events. Median survival time in eligible cases was 246 days (95%CI: 193–306+ days).

Conclusion: Oral administration of Capecitabine with the dose of 1657 mg/m² for 3-weeks-on and 1-week-off exhibits anti-tumor activity with a favorable safety profile and warrants further investigation.

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PUBLICATION

Phase II study of gemcitabine (GEM) combined with radiation therapy (RT) in localized, unresectable pancreatic cancer

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Purpose: To evaluate the efficacy and safety of GEM combined with RT in patients (pts) with localized, unresectable pancreatic cancer.

Methods: Weekly GEM at a dose of 1000 mg/m² for seven weeks was given initially, in order to provide clinical benefit (CB) and to select non-progressing pts for entering into the chemoradiotherapy (CRT) phase of the treatment. This consisted of GEM 400 mg/m² weekly \times 3 every 28 days for 2 cycles, delivered concurrently with RT to a total dose of 50.4 Gy in 1.8 Gy daily fractions. GEM dose was re-escalated to 1000 mg/m² after completion of RT.

Results: Between 8/97 and 12/98, 15 pts entered this study. Their median age was 65 y (38–84 y) and median performance status (PS) was 2 (1–3). Seven pts (46%) achieved positive CB response, measured by pain relief, improvement in PS or weight gain, and one pt was stable. Objectively, they had no tumor progression and thus enrolled to the CRT phase, followed by GEM alone. Five of them (33% of all pts) are alive and asymptomatic 10 m+ to 19 m+ after start of treatment, having objective partial response (2), minimal response (1) and no change (2). Overall median survival was

13 m, and it has not been reached yet for the CRT group. Grade 3/4 toxicity (nausea, vomiting, diarrhea) during CRT was noted in 3 pts, and neutropenic fever in one.

Conclusion: This schedule of GEM and RT is well tolerated and can provide prolonged CB response and local control in pts with localized, unresectable pancreatic cancer.

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PUBLICATION

Significant improvement of response rate and survival with cisplatin, epirubicin, 5-fluorouracil and gemcitabine (PEF-G regimen) in metastatic pancreatic cancer

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Purpose: To assess the efficacy of PEF-G regimen by comparing response rate (RR), time to treatment failure (TTF) and overall survival (OS) with three other chemotherapy (CHT) regimens in metastatic (M1) cancer of exocrine pancreas.

Methods: In the period 1981–98, four consecutive clinical prospective trials were performed in 114 patients selected according to the following criteria: histologic diagnosis of exocrine pancreatic cancer; M1 disease; age 18–70 years; ECOG PS < 2; normal bone marrow, hepatic and liver function; no previous CHT. Twenty-two patients (1981–88, median age 59 ys) received FAM regimen (5-fluorouracil 600 mg/m² days 1, 8, 29 and 36; adriamycin 30 mg/m² days 1 and 29; mitomycin 10 mg/m² day 1); 41 patients (1989–93, median age 55 ys) were treated with EF (epirubicin 50 mg/m² day 1; 5-fluorouracil 1 g/m² days 1 to 5); 22 patients (1994–96, median age 58 ys) received PEF (EF plus cisplatin 50 mg/m² day 1) and 29 patients (1997–98, median age 58 ys) received PEF-G (cisplatin and epirubicin 40 mg/m² day 1; 5-fluorouracil 200 mg/m²/day continuous infusion and gemcitabine 600 mg/m² days 1 and 8). All patients enrolled were considered for an intent-to-treat analysis. Response to CHT was assessed every 2 courses by CT scan.

Results: PEF-G compared favourably with the other three regimens for RR, TTF and OS, while no significant differences were detected among FAM, EF and PEF.

	FAM	EF	PEF	PEF-G	p
CR + PR (WHO criteria)	9%	2.5%	13.5%	62%	<0.0001 [†]
Median TTF (months)	2	2.5	2.5	5	0.0002 [°]
6 months progression-free	5 + 4%	10 + 5%	29 + 10%	42 + 11%	
Median survival (months)	5	5	7	6.5 +	0.009 [°]
1-yr survival rate	9 + 6%	9 + 5%	5 + 5%	27 + 11%	

([†] chi square [°] log-rank)

Conclusions: Even if these results should be confirmed in a larger series, PEF-G seems to be more effective than other CHT regimens in metastatic pancreatic cancer. Due to the significant improvement in RR, TTF and OS, PEF-G could become the first choice CHT regimen in pancreatic cancer.

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PUBLICATION

Periampullary carcinoma: Impact of adjuvant chemoradiotherapy on outcome

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Purpose: To evaluate the role of adjuvant chemoradiotherapy in periampullary carcinoma.

Methods: From 1989–1998, 66 patients of periampullary carcinoma were evaluated. All the patients underwent whipple's procedure. 45/66 (68%) patients received post-op adjuvant chemoradiation. Radiotherapy was given in doses of 45–50 Gy/4–5 wks with 5-FU 500 mg IV weekly × 12 wks. The patients with histological features of poorly differentiated, positive resection margin, lymph node & infiltration into pancreas were considered as high risk.

Results: 5-year estimated overall survival was 26% in adjuvant group versus 11% in surgical group. High risk patients with chemoradiation had 5-year survival of 16% vs 5% surgical group.

Conclusion: High risk group patients had high local failure rate and so require post-op adjuvant therapy. A prospective randomized control trial is needed for confirmation.

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PUBLICATION

Long term results with the surgical treatment of resectable gastric cancer

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Surgery remains as the only effective treatment of gastric cancer. Between January 1986 and December 1990, 279 patients were treated in the Clínica Oncológica I of the Portuguese Institute of Oncology-Porto

Fifty eight per cent were male and 42% female. Age was over 60 years in 65% of the patients.

Tumor location was: distal 1/3 – 103, middle 1/3 – 47, proximal 1/3 – 66, diffuse 63. The predominant treatment was surgery in 228 cases, chemotherapy in 10 cases and symptomatic in 41 cases.

Results: The overall 5-year survival rate was 48% for patients submitted to gastric resection. Depth of the tumor was an important prognostic factor with a 5-year survival of 90%, 70% and 32% for T1, T2 and T3, respectively. Lymph node metastasis was also a significative prognostic factor with a 5-years survival of 72% for N⁻ and 22% for N⁺. Location of the tumor and type of surgical resection do not alter the prognosis.

Conclusion: Gastric resection is a potentially curative procedure and is compatible with a long term survival.

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PUBLICATION

Submucosal tumors of the esophagus: Diagnostic role of endoscopic ultrasonography

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Background and Aims: The diagnosis of submucosal tumors of the esophagus by endoscopic ultrasonography (EUS) is based on their relation to the five-layer sonographic pattern of the normal esophageal wall produced by a radial scan transducer. Preliminary reports have suggested that this modality may be useful in imaging the esophageal wall more accurately than other imaging techniques. The aim of this study was to define the usefulness of EUS in the diagnosis of submucosal tumors of the esophagus and in the determination of their size, location and histological nature.

Patients and Methods: From June 1997 to January 1999 at the Endoscopy Service of the Institute of Clinical Oncology – University of Messina, 23 consecutive patients, 13 males and 10 females, ranging from 36 to 71 years of age (median age 56.1), with endoscopically proven esophageal submucosal tumor, were included in this study. We use an ultrasound endoscope with a radial-scan transducer which offers a choice of 7.5 MHz or 10 MHz scanning frequencies (Olympus GF-UM2/EUM2).

Results: Using EUS we diagnosed 21 cases of leiomyoma and 2 cases of leiomyosarcoma confirmed histologically. The EUS appearance was that of a hypoechoic mass arising in the fourth hypoechoic layer corresponds to the muscularis propria. Tumor diameter ranged from 5 to 35 mm. In all two cases of leiomyosarcoma, the size of the tumor was larger than 20 mm in diameter. No complication was encountered during this study.

Conclusions: Our findings are in accord with the existing literature and confirm the usefulness of EUS in the evaluation and in the diagnosis of submucosal tumors of the esophagus. In particular, due to its definition power, it gives accurate informations about size, location and nature of the esophageal intraparietal lesions.

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PUBLICATION

Cisplatin /5-FU (DDP/FU) as 2nd-line chemotherapy after CPT-11 (Irinotecan) failure for patients with metastatic gastric adenocarcinoma

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Purpose: Currently there are no data for chemotherapeutic options after tumor progression during CPT-11 therapy for metastatic gastric adenocarcinoma (MGC).

Method: A retrospective analysis was performed to determine the response rate and symptom control of pts with MGC treated with a 2nd-line DDP/FU combination after tumor progression while receiving CPT-11 single agent as 1st-line therapy. Data from 10 pts could be evaluated so far. All