PG 2.03 SPEAKER ABSTRACT

Lessons from PETACC3 in adjuvant treatment of colorectal cancer: today's impact

A. Roth. *Hug, Oncosurgery Unit, Geneva, Switzerland*

TNM staging remains so far the only validated tool to determine which patient might benefit from adjuvant systemic therapy. Pronostic markers allowing to better select which patient operated on from colon cancer could benefit from additional treatment are still missing. The clinical trial in post-operative treatment of colon cancer PETACC 3 enrolled 3,278 patients and collected the pathological material of 1564 of them for the study of new molecular pronostic factors. In addition to the ability to validate some already known potential pronostic molecular markers, we performed new tests to insulate mutations of the genome of the tumor and to study their genomic expression. The integration of some of these markers into the TNM staging suggests that we might be able to define new subpopulations of patients with distinct prognosis which still need to be validated in independent cohorts of patients. The implications of these results in the light of other published gene expression signatures aimed at improving prognosis prediction of stage II and III colorectal cancer to better select patients more likely to benefit from adjuvant systemic therapy shall be discussed.

PG 2.04 SPEAKER ABSTRACT

Systemic treatment of CRC: Molecular profiles ready for clinical practice?

S. Tejpar. *Universtiy Hospital Gasthuisberg, Leuven, Belgium*

Colorectal cancer is very heterogeneous disease, possibly even different diseases hitting the same organ. This has huge implications for clinical practice and the development of anti cancer drugs in this disease. Only two biomarkers for colorectal cancer are currently sufficiently validated for the clinic. Efforts to find genetic patterns that distinguish between tumours with good or poor prognosis or between patients who do or don't responder to various therapies are proceeding slowly but steadily. We will discuss various approaches, using cell lines, mouse models, patient tumors, that can provide key information. Key examples will be discussed, such as the identification of response signatures to EGFR inhibitors in colon cancer, or understanding the role of oncogenic BRAF in this disease, to highlight both gains and gaps in our knowledge. We will also discuss how lack of knowledge hampers current drug development and the challenges faced by both pharma and academia in developing successful trials, balancing biomarker identification and validation in this disease.

Thursday, 22 March, 12:00–12:30

Keynote Lecture I

PG 3.01 SPEAKER ABSTRACT

Cancer stem cells: the new target

R. Fodde. *Pathology, Erasmus MC, CA Rotterdam, Netherlands*

Cancer stem cells (CSCs) represent a subpopulation of tumour cells endowed with self-renewal and multi-lineage differentiation capacity but also with an innate resistance to cytotoxic agents, a feature likely to pose major clinical challenges towards the complete eradication of minimal residual disease in cancer patients. Operationally, CSCs are defined by their tumour-propagating ability when serially transplanted into immune-compromised mice and by their capacity to fully recapitulate the original heterogeneity of cell types observed in the primary lesions they are derived from. CSCs where first identified in hematopoietic malignancies and later in a broad spectrum of solid tumours including those of the breast, colon and brain. Notably, several CSCs' characteristics are relevant to metastasis, such as motility, invasiveness and, as mentioned above, resistance to DNA damage-induced apoptosis. Here, the relation between colon CSCs and metastasis formation will be discussed. Preliminary studies on cancer cell lines and patient-derived material suggest a rate-limiting role for stem-like cells in the processes of tumour cell dissemination and metastasis formation. However, additional studies are needed to deliver formal proof of their identity as cell of origin of recurrences at distant organ sites. Nevertheless, several studies have already provided pre-clinical evidence of the efficacy of novel therapies directed against disseminated CSCs.

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Thursday, 22 March, 14:00–15:30

Session III. Improving Treatment of Pancreatic Cancer

PG 4.01 SPEAKER ABSTRACT

Neoadjuvant approaches to pancreatic cancer

M. Lesurtel[1], B. Pestalozzi[2], P. Clavien[1]. *[1]Visceral & Transplantation Surgery, University Hospital of Zurich, Zürich, Switzerland, [2]Oncology, University Hospital Zurich, Zürich, Switzerland*

Despite major improvements in the perioperative outcome of pancreas surgery, the prognosis of pancreatic cancer after curative resection remains poor. Adjuvant chemotherapy increases disease-free and overall survival, but this treatment cannot be offered to 20% to 40% of patients due to the surgical morbidity. In contrast, neoadjuvant therapy has a substantial impact in several gastro-intestinal malignancies and has many theoretical advantages over adjuvant treatment in patients with pancreatic cancer. Neoadjuvant treatment has been proposed to have greater benefits on well oxygenated, non-devascularized tissue, with improved delivery of chemotherapeutic agents. It may be better tolerated, allowing for greater completion rates and may also reduce any delay in therapy, and could potentially downstage unresectable tumors. However, no phase III trials are available examining this approach in pancreatic cancer. Only prospective phase II trials using neoadjuvant treatment (chemotherapy or radio-chemotherapy) for resectable, borderline rsectable and unresectable pancreatic cancer are available. Based on these studies, neoadjuvant treatment seems to have some activity in patients with borderline/unresectable pancreatic cancer. Nearly one third of tumors initially deemed marginal for operative intervention could be resected after treatment. In case of initially resectable pancreatic tumors, it is not clear whether patients may benefit from neoadjuvant therapy. In a recent phase II trial we have shown that neoadjuvant Gemcitabine-Oxaliplatin is safe and effective, and has resulted in a median survival of 26.5 months. Moreover, it improved the nutritional status of patients with pancreatic cancer. We have therefore initiated a multicenter prospective randomized phase III trial (NEOPAC) to explore the efficacy of neoadjuvant chemotherapy in patients with pancreatic cancer. Patients with resectable, cytologically proven, adenocarcinoma of the pancreatic head are eligible for this study. An infiltration of the superior mesenteric vein >180º or major visceral arteries are considered exclusion criteria. Eligible patients are randomized to surgery followed by adjuvant gemcitabine (1000 mg/m^2) for 6 months or neoadjuvant chemotherapy followed by surgery and the same adjuvant treatment. Neoadjuvant chemotherapy (gemcitabine 1000 mg/m^2, oxaliplatin 100 mg/m^2) is given four times every two weeks. The staging as well as the restaging protocol after neoadjuvant chemotherapy includes computed tomography (or PET-CT if available) of chest and abdomen and diagnostic laparoscopy. The primary study endpoint is progression-free survival. According to the sample size calculation, 155 patients need to be randomized to each treatment arm. Disease recurrence will be documented by scheduled computed tomography scans 9, 12, 15, 21 and thereafter every 6 months until disease progression. For quality control, circumferential resection margins are marked intraoperatively, and representative histological sections will be centrally reviewed by a dedicated pathologist. The NEOPAC study will determine the efficacy of neoadjuvant chemotherapy in pancreatic cancer for the first time and offers a unique potential for translational research. Furthermore, this trial will provide the unbiased overall survival of all patients undergoing surgery for resectable cancer of the pancreatic head (clinicalTrials.gov NCT01314027).

Reference(s)

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PG 4.02 SPEAKER ABSTRACT

Pancreatic surgery: Beyond the traditional limits

B. Schmied, S. Müller, I. Tarantino. *Department of Surgery, Kantonsspital St. Gallen, St. Gallen, Switzerland*

Pancreatic cancer is the fourth leading cause of death in male and female in the western world. Pancreatic surgery with complete resection of the tumor is the only curative approach for pancreatic cancer at this time. In more than 85% pancreatic tumors are of ductal origin but cystic tumors such as

intrapapillary mucinous tumors (IPMN) or mucinous cystic tumors (MCN) and other rare tumors are increasing. However, in almost 40% of the patients with potentially resectable pancreatic cancer surgery is not offered, although 5-year survival rates are up to 40% or even higher in selected patients depending on tumor stage and histology [1]. Therefore surgicals kills and techniques and the perioperative management have to be improved to obtain curative resection and increase survival. Further factors influencing the outcome are the hospital volume and surgical experience [2]. Standard procedures for tumors in the head of the pancreas are the Kausch–Whipple- or pylorus-preserving Whipple procedure including local lymphadenectomy. For tumors left to the portal vein the procedure of choice is the left lateral pancreas resection, generally including lymphadenectomy and splenectomy. Whereas pancreatic fistulas after a Whipple procedure is as low as 2% in experienced hands [3], the fistula rate after left resection increases up to 40% depending on the technique used. Indications for extendend pancreatic surgery are increasing including venous and arterial infiltration, involvment of surrounding organs indicating multivisceral resections and surgery for metastatic disease or palliative pancreas resection. Nowadays, portal vein resection for local infiltration with or without replacement by a graft is established without change of mobidity or mortality or an increased rate fo R1 resection. Although arterial resection is in many cases technically feasable its oncologic impact remains questionnable and is reserved to rare indications. Although the value of extended lymphadenectomy is frequently debated, recent studies show no advantage (evidence level I) [4]. Multivisceral resections, i.e. in tumors of the tail of the pancreas invading the colon or stomach or other surrounding tissues are associated with an increased and a longer stay in the hospital. But they show comparable mortality- and survival rates to those without infiltration and therefore should be performed if technically feasable [5]. Data of surgical treatment in patients with metastatic pancreatic diesease do not show any advantage to palliative treatment but can be an option in selective patients with easily removable metastasis. Although some data indicate an increased 2-year survival for patients with palliative resection (R2) due to those only with palliative surgery (bypass surgery) it does not justify its increased morbidity and mortality and especially loss of quality of life [6]. Cystic tumors of the pancreas are increasing, probably due to earlier detection by high resolution imaging. Serous cystic tumors rarely become malignant and therefore do not need surgery except they become symptomatic. Due to its high malignant potential mucinous cystic tumors (MCN) should generally be operated such as main-duct IPMN's. Branch-duct IPMN have to be operated when they are larger than three centimeters or when thy show nodal involment or signs of malignancy. Parenchyma sparing procedures such as enucleation are reserved for benign diseases i.e. cystic tumors (branch-type IPMN). In conclusion pancreatic surgery beyond the traditional limits is established in tumors infiltration the venous system and may be an approach in patients with locally infiltratiing pancreatic cancer or metastasis but is not an option for palliative surgery.

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PG 4.03 SPEAKER ABSTRACT

Adjuvant therapy in resected pancreatic cancer

J.P. Neoptolemos. *University of Liverpool, Liverpool Cancer Research UK Centre, Liverpool, United Kingdom*

Resection rates of above 15% can be achieved in specialised centres with 5y survival rates of 10% and can be improved to 25−30% with adjuvant systemic chemotherapy. GITSG randomised 43 patients between chemoradiation (40 Gy with weekly 5-Fluorouracil (5FU) for two years) vs. surgery alone [1]. Median survival was increased in the treated group (20m vs. 11m, $p = 0.035$). The ESPAC1 trial was the first adequately powered, randomised study in resected pancreatic cancer [2]. Initial analysis of all 541 patients indicated no survival benefit for adjuvant chemoradiotherapy but the results for chemotherapy were inconclusive with only ten months' median follow-up. The final results of this trial in the 289 patients restricted to the original 2×2 factorial design definitively demonstrated a survival benefit for chemotherapy, but not for chemoradiotherapy [3]. The 5 y survival for chemoradiation was 10.0% and 19.6% without ($p = 0.05$) and 21.1% for chemotherapy and 8.4% without ($p = 0.009$). Quality of life improved after adjuvant therapy irrespective of the modality or combination of modalities [4]. A survival advantage was also demonstrated for adjuvant combination chemotherapy using 5FU, doxorubicin and mitomycin C in another randomised controlled trial [5]. A metaanalysis using individual patient data showed that the survival benefit of adjuvant chemotherapy extended to patients with R1 resection margins although the treatment effect was much less [6]. The EORTC randomised 218 patients (104 with ampullary tumours) to adjuvant chemoradiation (but with no follow-on chemotherapy) vs. surgery alone but survival was not improved [7,8]. The RTOG9704 trial randomised 538 patients to either pre- and post-chemoradiation gemcitabine or to pre- and post-chemoradiation 5FU [9]. The median survival in the 451 'eligible' patients was 16.7 mo and 18.8 mo respectively ($p = 0.34$) and in the 388 patients with pancreas head cancer 20.5 mo vs. 16.9 mo ($p = 0.09$). In the CONKO-001 trial DFS was 13.4 mo for gemcitabine and 6.9 mo for surgery alone ($p < 0.001$); median overall survival was 22.1 mo and 20.5 mo respectively ($p < 0.06$) [10]. A Japan trial which enrolled 119 patients showed longer DFS for gemcitabine than surgery-only (median 11.4 versus 5.0 mo; $p = 0.01$) [11] but not overall survival (22.3 versus 18.4 mo; $p = 0.19$). The ESPAC3 trial randomised 1088 patients to 5FU and folinic acid (FA) or to gemcitabine [12]. Median (95% CI) survival of patients treated with 5FU/FA was 23.0 mo (21.1, 25.0) and 23.6 mo (21.4, 26.4) for gemcitabine ($p = 0.39$; 0.81, 1.08). There were no differences in either DFS or global quality of life scores. Thus, there were no significant differences between the two treatments although adjuvant gemcitabine had an improved safety profile. Using individual patient data from both ESPAC1 and ESPAC3 a composite data analysis confirmed that adjuvant 5FU/FA had a significant survival benefit compared to observation for patients with pancreatic cancer [13]. Two major Editorials have supported the conclusions of the ESPAC trials and raise very serious questions about the continued use of adjuvant chemoradiation [14,15]. ESPAC4 trial is comparing combination chemotherapy with gemcitabine plus capecitabine with gemcitabine alone [16]. There is already rapid recruitment with sites throughout the United Kingdom, Sweden, France and Germany.

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PG 4.04 SPEAKER ABSTRACT

Radiochemotherapy of the pancreas: State of the art 2012

F. Mornex, O. Diaz, C. Enachescu. *Radiation Oncology, Centre Hospitalier Lyon Sud, Pierre Benite, France*

Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer-related mortality and is associated with an extremely poor prognosis, reflected by a median survival of 5−8 mo and a 5-y survival probability of less than 5% when all stages are combined. Currently, the only chance for cure and prolonged survival is surgical resection with macroscopic tumor clearance. However, only approximately 10%-20% of patients are candidates for curative resection. The majority of patients (50%-60%) present with metastatic disease, and thus palliative chemotherapy remains the only option for almost all of these patients [1]. Radiotherapy has a large role to play in the therapeutic management of this disease,

1. As a neoadjuvant approach for locally advanced resectable or borderline resectable tumors, most of the time in combination with chemotherapy. In a substantial number of patients (approximately 30%-40%) the disease is considered "locally advanced" at the time of diagnosis. This group of patients has been intensively discussed during the last years and neoadjuvant therapies have been proposed to achieve better local tumor control or tumor down-staging with a subsequent potentially resectable tumor [2]. Neoadjuvant therapy in this context is defined as any preoperative therapy aiming to convert unresectable to resectable tumors and/or to increase microscopic complete tumor resection rates [3, 4].
2. As an adjuvant approach, for R0 and/or R1 resected tumors, according with the literature.
3. For locally advanced unresectable tumors, in order to aim to cure the disease [5].
4. As a symptomatic treatment, either locally in case of local pain, or for a compressive effect relief, or for treating metastases.

In all these situations, radiotherapy benefits of the technical improvements like IGRT (Image Guided Radiation Therapy) which helps improving the tumor location immediately before and even during radiation delivery, for an optimal tumor targeting [6], like IMRT (Intensity Modulated Radiation Therapy) for