934

## Hepatic arterial therapy-is the concept dead or alive?

Abstract not received.

935

## Intraperitoneal chemotherapy in the management of ovarian cancer

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The intraperitoneal (IP) administration of cytotoxic agents is based on sound anatomic, physiologic and pharmacokinetic considerations. Phase 1 trials have demonstrated the safety of delivering a number of antineoplastic agents by this route, and have confirmed increased exposure for the peritoneal cavity (compared to the systemic compartment) ranging from 10-fold (e.g., cisplatin, carboplatin) to > 1000-fold (e.g., paclitaxel). Phase 2 second-line ovarian cancer studies have documented the ability of regional drug delivery to achieve surgically-documented complete responses, with activity being observed almost exclusively in those patients with microscopic or very small volume macroscopic disease (maximum diameter of residual tumor masses < 0.5-1 cm) when IP therapy is initiated. Two previously reported randomized trials comparing IP cisplatin to intravenous cisplatin as initial chemotherapy of small volume residual advanced ovarian cancer have confirmed a survival advantage associated with this approach. Despite this fact, IP therapy is rarely considered for routine clinical use, possibly due to concerns for technical difficulties associated with regional drug delivery and the apparent (but possibly incorrect) conclusion that cisplatin must be utilized, rather than carboplatin for IP treatment of ovarian cancer. Currently available data strongly supports further exploration of IP drug delivery, both as an initial and second-line treatment strategy for ovarian cancer.

936

## Intratumoral treatment

Abstract not received.

937

## Isolated limb perfusion: Lessons from preclinical models

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Isolated Limb Perfusion (ILP) with melphalan has a more than 30 year tradition as the treatment of choice of multiple melanoma in-transit metastases with overall complete response (CR) rates of about 50%. It has however failed in the treatment of large limb threatening extremity sarcomas. Since the use of Tumor Necrosis Factor-alpha (TNF) this situation has completely changed. Now, ILP with TNF + melphalan is a new, very successful EMEA-approved option in the management of extremity tumors to prevent amputation.

New data from experiments in our laboratory on the effects of TNF in isolation perfusion system has provided new insight in the synergistic antitumor effects that are seen in these systems when TNF is used in combination with melphalan or doxorubicin. A number of crucial observations about prerequisites for optimal effects of TNF have been identified; apart from the vasculotoxic effects on the tumor vasculature which leads to the selective destruction of tumor-associated vessels, a most essential mechanism has been discovered in our animal models: addition of TNF to the perfusate results in a highly significanty increased drug uptake (melphalan or doxorubicin) in tumors (3–6 fold). Similar synergy is observed in the treatment of well vascularized liver metastases by isolated hepatic perfusion with TNF and melphalan. New (vaso-active) drugs and new mechanisms of action are being discovered. We have also demonstrated that ILP is a promising treatment modality for adenoviral vector mediated genetherapy. Many new developments in the field of ILP can be expected for early clinical phase I–II evaluation

938

## Molecular markers of pancreatic cancer

Abstract not received.

939

## Pancreatic cancer surgery – The chance to be cured: Who benefits?

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The prognosis of patients suffering from pancreatic cancer is significantly related to the degree of cancer dissemination; on the basis of histopathological classification patients with pancreatic cancer, tumor size less than 2 cm, without lymph node metastases, without extrapancreatic nerve infiltration, without vessel wall infiltration and with cell differentiation grade I have a 30–50% chance to get cured by an R0-resection. On the basis of the UICC classification only patients with UICC stage I and II are candidates for surgery who have benefits from oncological resection. On the basis of the Ulm experience, 1000 patients with pancreatic cancer were managed surgically (5/1982–3/2001). 2.5% were UICC I, 6.2% UICC II, and 14.6% UICC III. Only 23.3% of the patients had a cancer stage without lymph node metastasation. Hospital mortality in 427 patients after resection was 2.3%. 60% of the patients had an uneventful postoperative course without any local or systemic complications. Patients who had an R0-resection had a 5-year survival chance of 28%. Patients with an R1/R2-resection had an actuarial survival of less than 10%. All patients after pancreatic cancer resection should have adjuvant chemotherapy which leads, on the basis of the ESPAC trial (*Lancet* 2001), to an additional significant survival benefit.

**Conclusion:** Patients in cancer stages UICC I, II and III have a survival benefit from oncological resection if an R0-resection has been performed: adjuvant chemotherapy is recommended in every case after surgical resection, leading to an additional survival increase.

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## ESPAC-1: A European, randomised study to assess the roles of adjuvant chemotherapy and chemoradiation in resectable pancreatic cancer

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Pancreatic cancer affects 8–12 per 100,000 population per year in Europe and North America. Post-resection, long term survival is 10–15%. ESPAC-1 is the largest randomised adjuvant pancreatic study designed to answer: (i) is there a role for chemoradiation (40 Gy + 5-fluorouracil); (ii) is there a role for chemotherapy (5-fluorouracil + folinic acid). 541 patients with pancreatic ductal adenocarcinoma were randomised from 83 clinicians in 11 countries. Presently, 227 patients (42%) are alive with median follow-up of 10 months (inter-quartile range 1–25). Preliminary results show no evidence of a survival benefit for chemoradiation treatment (median survival 15.5 months with chemoradiation vs 16.1 months without, $p = 0.24$). There is evidence of a benefit for patients having chemotherapy (median survival 19.7 months with chemotherapy vs 14.0 months without, $p < 0.001$). Secondary endpoints include QoL which was assessed by patient questionnaires (EORTC QLQ-C30/ESPAC-QLQ32) completed at 3 monthly intervals. The 15 QoL dimensions measured by the questionnaire were analysed. A total of 296 patients have completed 789 questionnaires within 1 year of entry. Changes in dimension scores within 6 months from entry were compared between treatments. Initial analysis suggests that, for 3 of the 15 dimensions (social functioning, appetite and constipation), the change over time differs depending upon treatment.

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## Outcomes trial demonstrating a survival advantage of initial chemoradiotherapy for regional pancreatic adenocarcinoma (PCa)

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**Background:** Resection of PCa, traditionally considered the patient's only chance for cure, is resource-intensive with limited impact on survival.

Chemotherapy and/or radiotherapy (RT) have been shown to have some effect for palliation, but its use is inconsistent. Accurate diagnosis and staging of PCa can be done in almost all patients without surgery. To examine the outcome on survival of neoadjuvant chemoRT, patients with a regional PCa with a minimal chance of being resected successfully received chemoRT, and were compared to patients with resectable disease who had all visible tumor surgically removed.

**Methods:** Patients with radiologically regional tumors were staged by laparotomy and/or computerized tomography followed by endoscopic ultrasonography, angiography and/or laparoscopy. Those with locally invasive, inresectable, regional PCa were initially treated with simultaneous split-course radiotherapy plus 5-fluorouracil, streptozotocin, and cisplatin (RT-FSP), followed by selective surgery (Group-1). Patients determined to have a resectable tumor initially underwent resection without preoperative chemoradiotherapy, with or without postoperative chemoradiotherapy (Group-2).

**Results:** Over 8 years, 159 patients presenting with nonmetastatic PCa were administered RT-FSP or underwent surgery for resection. Group-1, comprised of 68 patients initially treated with RT-FSP had a 0% mortality rate within 30 days of entry. In 20 of 30 undergoing surgery after RT-FSP, tumors were confirmed as downstaged and resected. Group-2, comprised of 91 patients who initially underwent successful resection, had a 5% mortality rate within 30 days of entry. Postoperatively, 63 of these patients received chemotherapy with or without RT. Medial survival for Group-1 was 22.8 mo compared with 14.1 mo for Group-2 (Log-Rank $p = 0.005$) despite more advanced disease cases in Group-1. Survival favored RT-FSP regardless of whether lymph nodes were malignant. The dominant prognostic factor of earlier stage carcinoma having an expected survival advantage was reversed by initial nonoperative neoadjuvant treatment. There were 8 disease-free 5-year survivors in the initially unresectable Group-1 patients compared with only 1 in resectable Group-2 patients (mean follow-up of patients alive >6 yr.) In 43 patients in whom 42% had tumors that appeared resectable, and who declined initial treatment except for palliation of any biliary obstruction (Group-3), there were no 5-year survivors; median survival was only 8.4 mo ($p = 0.0001$).

**Conclusions:** Based on a reversal of the expected trend that patients with earlier stage resectable PCa (T:1,2; N:0,1; M:0) who undergo removal of their tumors survive longer than patients with more advanced regional disease (T:3; N:0,1; M:0), survival was found to improve significantly for patients reliably staged as having locally invasive, unresectable, nonmetastatic PCa when initially treated with RT-FSP. Initial neoadjuvant therapy appears to result in a cue of at least 10% for patients with regional PCa.

942

## Neoadjuvant radiotherapy: drugs or rays? Hypo- or hyper-?

K. Haustermans. *UZ Gasthuisberg, Department of Radiotherapy, Leuven, Belgium*

Adenocarcinoma of the pancreas is a devastating disease. Only approximately 20% of patients are operable at the time of diagnosis. Median survival of this selected patient group is 12 months. Patients die of both loco-regional recurrence and distant metastases. The risk of subclinical metastasis at the time of primary surgery prompted clinicians to initiate studies in which chemo-radiotherapy is given preoperatively. In this way, patients with disseminated disease at the time of re-staging after chemo-radiotherapy will not be subjected to major surgery. Because of the large percentage of patients with disseminated disease, the improved loco-regional control achieved with preoperative chemo-radiotherapy followed by surgery will translate into only a small survival advantage. More effective systemic agents are therefore needed both to maximize radiation sensitisation and to more efficiently treat microscopic extra-pancreatic disease. As the median survival time of these patients is short, long treatments should be avoided. Several studies have investigated hypo-fractionated radiation giving large doses per fraction in a short overall treatment time combined mainly with 5-FU or Gemcitabine. To avoid the expected toxicity of large doses per fraction, an alternative to be explored is hyperfractionated, accelerated radiation. In addition, giving radiotherapy should not lead to less effective drug delivery. This can be avoided by limiting the size of the radiation fields with the aid of modern imaging techniques, enabling the radiation oncologist to accurately delineate target volumes, taking into account breathing movement of pancreas and kidneys. New phase I and II trials are investigating the combination of conventional chemo-radiotherapy with systemic delivery of novel biological agents targeting essential steps in tumor growth and progression, e.g. EGFR inhibitors. This lecture will give an overview of achievements and future prospects in the field of neoadjuvant chemo-radiotherapy in pancreatic cancer.

943

## ATM: From genotoxic stress to signalling networks

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The stability of the cellular genome is constantly threatened by errors in DNA metabolism as well as by internal and external DNA damaging agents. Defects in maintaining genome stability may lead to cell death or neoplasia. Thus, genetic disorders associated with defective DNA damage responses are usually characterized by genetic predisposition to disease ataxia-telangiectasia (A-T). A-T is characterized by cerebellar degeneration, immunodeficiency, genomic instability, radiation sensitivity, and acute predisposition to cancer, particularly the development of lymphoreticular malignancies. A-T cells are strikingly deficient in their responses to DNA double-strand break (DSB). A DSB is a critical DNA lesion, to which the cell responds by activating an extensive network of signaling pathways that span DNA repair, cell cycle checkpoints, and alterations in a variety of other processes. The ATM protein is a master controller of this network by virtue of its protein kinase activity. Upon the induction of DSBs in the DNA, a fraction of ATM becomes tightly associated with sub-nuclear structures and its kinase activity is enhanced. Following this enhancement, ATM immediately phosphorylates an extensive series of substrates, each of which in turn affects the activity of a certain signaling pathway or some aspect of the damage response. For example, ATM controls the G1/S cell cycle checkpoint by affecting the activation and stabilization of the p53 protein via a series of ATM-dependent post-translational modifications of p53 and the Mdm2 protein, which inhibits p53 and mediates its degradation. Other important targets of ATM-mediated phosphorylation are the BRCA1 and Nbs1 proteins, which are involved in several pathways of the damage response network. ATM is also involved in the modulation of the expression of numerous genes that are involved in many cellular processes. The immediate and wide ATM-mediated response to DNA damage may partly be explained by its association with large protein complexes that contain a diversity of proteins involved in many aspects of cellular metabolism. Thus, ATM represents a pivotal class of proteins that maintain genome stability by concerted activation of numerous cellular pathways in response to DNA damage. The acute cancer predisposition in A-T patients highlights the central role of inherited failure of this system in cancer predisposition.

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## Chromosomal instability and cancer predisposition: Insights from studies on the breast cancer gene BRCA2

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Germline mutations in the breast cancer gene BRCA2 predispose to early-onset, familial cases of breast and ovarian cancer. While inheritance of a single defective allele suffices to confer predisposition, loss of the second allele is consistently observed in cancer cells isolated from predisposed individuals, indicating that BRCA2 works in some respect as a tumour suppressor. BRCA2 encodes large, nuclear-localised protein products whose precise biological function remains enigmatic. Here, recent data will be presented to demonstrate that BRCA2 has an essential function in DNA repair by homologous recombination, whose integrity is required for the maintenance of chromosome stability. Loss of this function results in the spontaneous accrual of gross chromosomal rearrangements, showing that BRCA2 serves as a caretaker of genome stability whose disruption accelerates the acquisition of cancer-causing mutations. Targets for the secondary genetic events that foster the transformation of BRCA2-deficient cells have been identified, and their role in cancer predisposition will be discussed.

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## DNA repair defects and mouse models for cancer susceptibility

Abstract not received.