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.

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

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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.

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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.