857

Gastric cancer – How to improve results with a multimodal approach?

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Since more than 20 years, attempts were made to improve the unchanged poor prognosis of gastric cancer (GC) patients by combining surgery (S), chemotherapy (CTx) and radiotherapy (RTx). Such approaches include preoperative CTx ± RTx, intraoperative RTx or postoperative CTx ± RTx. Until now, postoperative (adjuvant) CTX or CTx/RTX could not show that they really improve the results as compared to S alone. This is at least true for trials conducted in Western countries. However, this doesn't mean that postop. approaches are generally inactive, because in most trials CTx regimens were used which nowadays would be regarded as only moderately active. Moreover the patient populations accrued in these trials were heterogeneous and surgical approaches as well as surgical quality controls frequently not well defined. Intraoperative treatments such as IORT or i.p. CTx have also not yet demonstrated that they may contribute to a better outcome. Currently the most promising multimodal approach is preoperative CTx or CTx/RTx. Most published trials dealing with this issue were phase II trials in patients with clinically staged "potentially" resectable or clinically staged locally advanced (LAD) GC. These trials show that preoperative CTx is feasible, does not increase perioperative mortality and at least in LAD appears to improve R0 resection rates and survival. However well designed clinically trials based on an appropriate staging (endoscopic ultrasound, laparoscopy) are still lacking but urgently needed in order to better define the possible role of preop. CTx in this situation. In patients whose tumor was defined as unresectable during an explorative laparotomy, preop. CTx clearly demonstrated its efficacy. An R0 resection rate of approx. 40–50% and long-term survival of 15–20% were reported after preop. CTx. Also of note were the first reports of preop. CTx/RTx in proximal (cardia) gastric cancer indicating that this might become another step ahead in the management of this challenging tumor.

858

Pancreatic cancer – Can we do better?

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Pancreatic cancer is the third leading neoplasm of the gastrointestinal system and represents one of the most aggressive human malignancies. Due to the late onset of clinical symptoms and the lack of accurate screening tests, the majority of patients are no more suitable for resection at time of diagnosis due to the presence of metastases or major infiltrations of the retroperitoneum. Oncological treatment modalities have failed so far to improve long-term results. Therefore, radical resection remains the only therapy with a chance for cure. For the surgical treatment of pancreatic head cancer, the classical Whipple operation is still the standard procedure but during the last two decades, the pylorus-preserving duodenopancreatectomy has been evolved as a more conservative procedure in order to omit the consequences of partial gastrectomy. For cancer of the pancreatic body and tail, distal pancreatectomy or total pancreatectomy may be indicated. With the advances in surgical technique and intensive care, the mortality rate has markedly decreased during the last two decades and averages around 5% in experienced centres. In contrast to these improvements, advances in long-term results are less obvious. A 5-year survival rate around 10% after radical resection of cancer of the pancreatic head is still considered the standard achievement and results for cancer of the pancreatic body and tail are even worse. So far, adjuvant treatment modalities have failed to demonstrate a significant benefit in a recent prospective and randomised trial. Moreover, more radical methods like regional pancreatectomy and resection with extended lymph node dissection could not improve long-term survival compared to the standard types of resection. For further advances in the treatment of pancreatic cancer, prospectively randomised trials are needed to compare these extended surgical procedures with the standard types of resection.

859

Multimodal treatment in colon cancer: Recent advances and future prospects

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Multimodal treatment is more and more frequent in the treatment of colon cancer, especially in adjuvant setting.

Adjuvant treatment: In approximately half of the patients treated surgically for colon cancer, incurable tumour recurrence can be expected. This has led to the development of adjuvant cytotoxic therapy. The role of 5FU + levamisole in stage III colon cancer was demonstrated in 1990. 5 years later, the combination of leucovorin + 5FU was proved to be effective with a significant reduction of mortality. The role of adjuvant systemic chemotherapy in lower-risk groups remains uncertain. Another way of multimodal adjuvant treatment of colon cancer is portal chemotherapy. After promising results, a meta-analysis and recent large studies have shown that the efficacy of intraportal chemotherapy was less than the efficacy of systemic chemotherapy. Question of its efficacy as a complementary method used in parallel with systemic chemotherapy is not solved. The future of multimodal adjuvant treatment of colon cancer can be broadly split into five categories: evaluation and reproducibility of surgical procedures, novel cytotoxic drugs: raltitrexed, oxaliplatin or irinotecan, specific or non specific immunotherapy, inhibitors of angiogenesis, gene therapy.

Metastatic disease: Recent results show that the resection of previously unresectable hepatic metastases became possible in up to 16% of patients after chemotherapy with oxaliplatin plus 5FU and leucovorin. Of the patients who had successful resections, 40% were alive at 5 years. After cytoreductive surgery of peritoneal carcinomatosis, intraoperative chemotherapy or chemohyperthermia and postoperative intraperitoenal chemotherapy have given promising results.

860

Preoperative radiotherapy is better than postoperative in rectal cancer

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Due to the high local recurrence rate in rectal cancer surgery, adjuvant treatment with radiotherapy has been proposed. However, the local recurrence rates differ substantially in literature, which might be one reason that adjuvant treatment is not obvious to all surgeons. This difference can be a matter of selection bias, different criteria for curative surgery, different follow-up routine, and/or the skill of the surgeon. Indisputable data from all randomized trials where surgery alone has been compared with surgery plus radiotherapy, either given pre- or postoperatively, is the average local recurrence rate of 29% in the surgery alone arm.

With pre- or postoperative radiotherapy the local recurrence rate is more or less halved. However, preoperative irradiation is more dose-efficient than the postoperative one, indicating that a higher dose has to be used if postoperative radiotherapy is delivered with an increased risk of damaging the normal surrounding tissues in the pelvis. This damage of the normal tissue also has an impact on sphincter function as well as on postoperative small bowel obstruction.

Due to the fact that preoperative radiotherapy is more effective on tumour cell kill at a lower dose than for postoperative treatment and with less toxic effects on normal tissues, preoperative radiotherapy should be used, if radiohterapy for rectal cancer is considered.

861

A big bullet for a big tumour? – Locally advanced rectal cancer

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Approximately 10% of primary rectal cancers are fixed to pelvic structures, making them unsuitable for primary surgery. Moreover, a considerable number of patients primarily operated for cure develop local recurrences which in most cases are located outside the rectum and fixed to the pelvic wall. These patients represent a real challenge to surgeons, oncologists and others. Treatment varies from simple symptom palliation via palliative radio- and chemotherapy to an aggressive curative approach including several treatment modalities.

Cure is possible to obtain in selected groups of patients, using a multidisciplinary approach. Thus, several reports conclude with 5-year survival rates of 40% and 20%, in primary and recurrent cases, respectively, provided a "radical" resection could be performed. In these studies preoperative external radiotherapy at a dose of 45–54 Gy (1.8–2.0 Gy/fraction) was combined with extensive surgery, in many cases also involving prostate, bladder and internal genitals. Less documentation exist regarding quality of life of these patients.

Chemotherapy in addition to radiotherapy and surgery is employed in many institutions, concomitantly with the irradiation and/or postoperatively,

although survival improvement has not been adequately documented. Intraoperative radiotherapy (IORT) is in some institutions given as a boost of 12–18 Gy to improve local control and survival. However, data from randomized studies are lacking and results obtained without IORT may be as good as those obtained with IORT. Hypertermia is currently being investigated in the same groups of patients.

How much should be given to obtain a high probability of survival and a good life quality? Current knowledge and practice will be discussed.

862

Dose/volume effects – The foundation of conformal radiotherapy

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3-Dimensional imaging and the development of advanced planning programmes and treatment delivery and verification techniques have enabled the clinical development of conformal, and now intensity modulated, radiotherapy. The clinician "knows" that reducing the amount of normal tissues irradiated in radical treatments must be beneficial, but quantification and modelling of potential advantages is not easy. There is controversy about how to handle data from inhomogeneous dose distributions and the validity of dose reduction algorithms. For tubular structures such as the rectum, dose volume (solid organ), dose surface, dose wall or dose contour histograms can be derived and the appropriate dose descriptor may change with endpoint studies. For example, different tissue organisation may be related most clearly to stricture (series) rather than rectal bleeding/proctitis (parallel). Data for dose response NTCP have been largely derived from pooled clinical data and a major aim in on-going trials must be the collection of high quality dose-volume-complication clinical data. Phase III studies in prostate cancer have now clearly demonstrated the presence of a significant volume effect. The challenge for the future is to document the benefit of dose escalation in increasing tumour control and develop user friendly models to guide, for example, the selection of optimal treatment techniques and margin as well as customised dose delivery.

863

Objective evaluation of tumor response of non-small cell lung cancer (NSCLC) after 70 Gy conformal radiotherapy using matched CT scan data

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Purpose: To evaluate tumor response, 16 patients were analyzed that were irradiated to a dose of 70 Gy in 35 fractions because of an inoperable NSCLC.

Methods: Three months after the end of irradiation a CT scan of the thorax was repeated conform the planning CT scan (in treatment position). The CT scan was matched to the pre-radiotherapy (pre-RT) planning CT scan using chamfer matching. On the CT scan "post-RT" the Gross Tumor Volume (GTV) was delineated and compared to the GTV "pre-RT". The GTV includes the primary tumor and pathologic lymph nodes plus abnormal findings detected on bronchoscopy and/or mediastinoscopy. The GTV "post-RT" was drawn with the spatial information of the matched CT scan "pre-RT".

Results: In two patients the GTV "post-RT" could not be defined because of the development of a pleural effusion in one patient and a massive atelectasis in the other patient. The mean GTV "pre-RT" was 106 cm3 (range 10–368 cm3) in these 16 patients. The GTV was not related with TNM stage. The GTV "post-RT" ranged from 0 to 86 cm3, with a mean of 29 cm3. The mean relative decrease in GTV in the 14 patients was 76% (range 46–100%). One complete response, 12 partial responses and one stable disease was objectively measured.

Conclusion: Matching CT scans is a helpful instrument to delineate and compare the GTV on the "post-RT" scan. It is useful to have spacial information to evaluate tumor reponse. In our current phase I/II dose escalation study a CT scan in treatment position is repeated to evaluate tumor response objectively.

864

Conformal radiotherapy and paediatric tumours

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The expected cure rate for children with cancer approaches 80%. The majority of these children are managed with multi-disciplinary approaches with a goal of cure without late consequences of therapy.

Prescribed doses for radiotherapy are limited by the radiation sensitivity of the surrounding normal tissue. Unique to paediatric radiotherapy is the sensitivity of rapidly growing/developing tissues, thus organ-specific tolerances are lower in children. Combined modality therapy further increases the radiosensitivity of normal tissues, potentially limiting radiation doses.

Three-dimensional conformal radiotherapy (3DCRT) improves the accuracy of targeting tumours while reducing the radiation exposure of normal tissues, allowing for dose escalation. High resolution CT scanners, CT and MRI image fusion, 3D reconstruction with beams-eye-view graphics, isodose distributions and dose-volume histograms are useful in constructing and evaluating treatment plans. Linear accelerators with dynamic multi-leaf and mini-multi-leaf collimators allow the delivery of even more conformal dose distributions. Inverse planning with intensity-modulated radiation therapy (IMRT) allows complex treatment while sparing tissues directly adjacent to the treatment volume. This most conformal treatment requires exquisite target and normal tissue delineation with precise patient positioning. For children, precise immobilization is crucial and often requires general anesthesia. Children have short attention spans thus requiting short treatment times. Young children with benign and malignant brain tumours, and soft tissue sarcomas such as rhabdomyosarcoma presenting in critical organs are most likely to profit from this new technology. Different techniques are being developed to minimize treatment duration for children. Quantitative studies comparing outcome, expense, and treatment time from routine, conformal, and IMRT plans in children are needed.

865

Intensity modulated radiotherapy with dynamic multileaf collimators. Technology and clinical potential

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Since early 1997, dynamic multileaf collimators (DMLCs) are used in our division for intensity modulated radiotherapy (IMRT). We have used IMRT to i) irradiate concave targets (head and neck, paraspinal tumors); ii) combine beams with shallow hinge angles (mediastinum, lung tumors); and iii) deliver intentionally inhomogeneous dose distributions (prostate, paranasal sinuses, brain tumors). IMRT is now our standard treatment for locoregional relapse (after high-dose radiotherapy) of head and neck cancer and for radical treatment of localized prostate cancer. For a variety of other tumors, conventional 3D-plans are compared with IMRT-plans, the latter being clinically implemented if superior.

We developed a geometry based IMRT planning strategy to create assemblies of static intensity modulated (IM)-beams which consist of uniform (unmodulated) segments. By a translator program, segments are combined in a single prescription which allows delivery under computer control. Cost-containment is further improved by automation of the planning. After manual or semiautomated contouring of PTV and the organs at risk, prostate IMRT plans, based on a class solution, are generated and optimized by a computer. IMRT for pharyngeal relapses and most other tumor sites is planned semi-automatically. IMRT replaces gradually conventional treatments in our division. Interesting dose distributions generated by IMRT allow better sparing of normal tissues with decreased acute and late toxicity and offer a window for further dose escalation.

866

Abstract not received.