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Advances in the treatment of cervical carcinoma: hemoglobin, hypoxia and concurrent chemo-radiotherapy

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Since the National Cancer Institute of the U.S. issued a rare clinical announcement in February of 1999, the use of weekly cisplatin chemotherapy concurrently with radical irradiation has become the standard of care in the management of patients with advanced cervical cancer. Five randomized trials and a meta-analysis have shown an overall survival benefit of 10-15% for the combined strategy. However many controversies remain with respect to optimal therapy of advanced cervical cancer. To be discussed will be the lack of data explicitly supporting weekly cisplatin as the concurrent treatment of choice, the apparent relative lack of benefit for some stages and extents of disease e.g. stage IIIB, the magnitude of incremental value when chemotherapy is added to optimized radiation, or given when para-aortic nodes are involved, and the lack of impact on distant metastases rates. A large randomized Canadian trial revealed no benefit from the use of weekly cisplatin; one large randomized trial using mitomycin and oral 5FU without cisplatin has shown a survival benefit; single agent epirubicin given concurrently and as adjuvant has also shown a survival benefit with a reduction in distant metastases. Thus, questions remain: what is the optimal chemotherapy agent(s) and schedule? Does adding chemotherapy to optimal radiation improve the therapeutic ratio? Do only some sets of patients benefit from concurrent chemotherapy? Will adjuvant chemotherapy in addition reduce distant metastases?

Additional strategies to improve the treatment of cervical cancer are based on overcoming the recognized negative effect of tumor hypoxia on response to radiation and chemotherapy. Hypoxia causes radiation and chemotherapy resistance and also induces genes which lead to angiogenesis and the development of a more aggressive tumor, phenotype. Low hemoglobin levels during radiation therapy are also associated with inferior local control and survival in cervical cancer. A retrospective Canadian study of over 600 cervical cancer patients treated with definitive pelvic irradiation revealed on multivariate analysis that hemoglobin levels during radiation treatment were second only to stage for prognostic importance. Survival was 25% better if the average hemoglobin was greater than or equal to 120g/l regardless of whether the patient started with high or low hemoglobin and received transfusion. Pelvic relapse was halved, and distant metastasis rates were significantly lower in those with high hemoglobin. Confirmatory data, as yet unpublished from the Gynecological Oncology Group, confirmed the importance of hemoglobin levels during concurrent cisplatin radiation treatment in over 400 patients. Thus although the relationship between anemia and hypoxia is unclear, both correlate with survival levels. Understanding these relationships and underlying mechanisms allows the development of possible interventions in the "hypoxia-hemoglobin" pathways to improve outcomes. These will be discussed.

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Chemotherapy and new approaches in cervical cancer

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The main players in the management of patients with CC have been and still are surgery and radiotherapy. The role of medical treatment, in the past merely used for palliation, has now become more promising when integrated in the primary treatment of the disease. It still can be concluded that there is no standard therapy for patients with recurrent/metastatic CC. Single agent cisplatin is a good option, but preferably such patients should participate in trials. With respect to the treatment of primary disease, neoadjuvant chemotherapy (NACT) followed by radiotherapy in patients with locally advanced disease cannot be recommended at the present time. The same is true for NACT followed by surgery, although some randomized trials suggest an improved outcome, in particular for patients with stage Ib2, IIa and IIb disease. Data on adjuvant chemotherapy are scanty and inconclusive. Chemoradiation is the new standard anno 2003 for patients, who otherwise would be treated with radiotherapy, based on several randomized trials and a meta-analysis. Novel strategies include the use of new drugs (taxanes, topo-I-inhibitors, vinca-alkaloids, gemcitabine), new combinations, dose dense therapies, the combined use of hyperthermia and chemotherapy, radiotherapy or both, the use of new cytotoxics or non-cytotoxics to enhance the effect of radiation therapy, methods to overcome hypoxia during radiotherapy and gene therapy.

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Quality control in surgical oncology: breast cancer

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The delivery of a quality service is of fundamental importance in the care given to patients presenting with cancer. The demand for such quality is led both by the medical and allied professions. The medical profession and societies which govern it are increasingly preoccupied with standards of care and are moving steadily towards systems which allow measurement of such standards on an individual basis as well as defining standards of care for institutions. Surgery is the mainstay of treatment for most solid tumours and as such quality control in surgical oncology is of fundamental importance in optimising disease free interval and survival. Other treatment modalities such as chemotherapy or radiotherapy cannot compensate for inadequate surgery.

The development of the concept of a specialist breast unit has been the single most important advance in recent years and the evidence is now clear that such a structure enhances quality of decision making and quality of patient care and as such will eventually impact on disease free interval and survival. Such a structure recognises the fundamental principle in the management of breast cancer that a multi-disciplinary approach is preferable to that where decision making is governed by one discipline alone. The surgical oncologist is pivotal in this context, as he/she is invariably the first point of contact along the care pathway in the hospital setting. It is the responsibility of the surgeon to diagnose breast cancer, to ensure that there is a multi-disciplinary team approach to decision making and to then introduce the patient into this process.

The triple assessment or rapid diagnostic clinic is the recognised method of establishing a diagnosis in symptomatic breast cancer. It is clear that quality control in diagnosis is not just an issue of quality of the surgical oncologist but also relates to many other quality issues including quality of radiography, quality of reporting of imaging and perhaps most importantly quality in fine needle aspiration cytology.

The determination of nodal status is a crucial issue in quality control in surgical oncology as this is the single most important prognostic indicator on which adjuvant treatment is based. Inadequate staging due to poor quality surgery will impact on disease free interval and survival. The advent of sentinel node biopsy has compounded matters and whilst axillary clearance still remains the gold standard, it is at odds with the current thrust towards a minimalist approach in surgical oncology typified by the breast conserving approach.

In summary the surgical oncologist has a pivotal role in the management of breast cancer in both surgical intervention and as the first point of contact at the breast clinic which acts as the platform on which the patients path is determined. As such, quality of patient care is governed by the technical excellence of the surgeon and his/her ability to coordinate the multidisciplinary approach to the patient at both diagnostic and therapeutic levels.

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Rectal cancer surgical quality – the key to effective multimodality treatment

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Rectal cancer poses a challenge to surgical, radiation and medical oncologists. One of the major problems in the treatment of rectal cancer has been the inability to achieve local control. Local failure is a serious problem which causes severe disabling symptoms that are difficult to treat and often kill the patient. In an attempt to improve local control and survival, many adjuvant treatment modalities have been investigated in the past. Results of studies that explored the role of radiotherapy showed that preoperative radiotherapy is more effective than postoperative radiotherapy in reducing

local recurrence rates [1]. Few years later, the Swedish Rectal Cancer Trial found that preoperative radiotherapy improved survival compared to surgery alone [2]. The results of a large meta-analysis strengthened the idea that adding preoperative radiotherapy to surgery could improve overall and cancer specific survival [3].

Apart from the advances in rectal cancer treatment through the introduction of effective adjuvant treatment regimens, the concept of adequate surgery has changed dramatically in recent years. It was discovered that the basic conventional procedure that involves blunt dissection of the rectal fascia failed to remove all mesorectal tissue, which was associated with high recurrence rates from 15 up to 45% [4]. The acknowledgement of the important role of circumferential margin involvement in the occurrence of local recurrences led to the introduction of TME (Total Mesorectal Excision) surgery [5]. By using sharp dissection under direct vision a relative bloodless plane is followed along the outer surface of the rectum. This technique ensures a specimen with intact mesorectum with negative tumour margins in the majority of resectable (i.e. mobile) rectal cancers. As was concluded from mainly retrospective studies, the use of this technique resulted in favourable local recurrence rates and increased survival compared to conventional blunt dissection.

Considering the progress in rectal cancer treatment in the areas of both adjuvant treatment and surgery, the question had to be answered whether adjuvant treatment in addition to TME surgery was still capable of achieving any further improvement in outcome. To answer this question, a large international multicenter trial was set up by the Dutch Colorectal Cancer Group together with the Nordic Gastro Intestinal Tumor Adjuvant Therapy Group and the EORTC to investigate the efficacy of short term preoperative radiotherapy in TME treated rectal cancer patients. From January 1996 until December 1999 1861 patients with histologically proven adenocarcinoma of the rectum without evidence of distant metastases were included into the study. 1861 patients were randomly assigned in one of the two treatment groups. The participating surgeons attended workshops and symposiums, saws instructional videotapes and were monitored by specially trained surgeons. Pathologists were trained to identify lateral spread of the tumour according to the protocol of Quirke et al. The local recurrence analysis for all patients of the TME trial showed a 2-year local recurrence rate of 5.3%. In the TME group this rate was 8.2% and in the RT+TME group 2.4% ($p < 0.001$). Survival rates did not differ significantly [6]. Macroscopic examination of the resected specimen correlated independently from gender, age and tumour size with local failure and survival [7]. In a univariate subgroup analysis, the beneficial effect of short term irradiation was not significant in patients who had lesions located more than 10 centimetres from the anal verge and in patients with TNM stage I and IV. However, diagnostic tools like digital rectal examination and endorectal ultrasonography are not capable of identifying these subgroups of patients accurately.

It became apparent from this study that performing a R0 resection is of utmost importance. Of 1759 eligible patients with available information on margins and tumour spillage, only 1351 (77%) had tumour-free margins. Patients with involved margins had significant worse local recurrence and survival rates than patients that did not. Moreover, preoperative radiotherapy had only a limited effect on the prevention of local recurrences in patients with positive resection margins. (8) It must be assumed that the number of tumour cells, still present in many patients with positive margins is too high to prevent local recurrences by giving preoperative radiotherapy. Furthermore, neither postoperative radiotherapy had a significant effect on the prevention of local recurrences in these patients. Postoperative adjuvant treatment can thus not compensate for suboptimal surgery. These findings stress the importance of adequate surgery. Preoperative imaging like MRI scanning may serve as good tool to select patients at risk for R1 resection. (9) These patients will benefit most likely from conventional neoadjuvant chemoradiation, which may lead to downstaging and downsizing, thus enabling a R0 resection. Improving this risk assessment in a preoperative phase will therefore lead to better treatment outcome for all patient subgroups with rectal cancer.

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Cancer of the oesophagus and gastro-oesophageal junction

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The lack of desired success in the surgical management of cancer of the esophagus and gastroesophageal junction has resulted into an interest to investigate preoperative and postoperative adjuvant therapies. The seemingly promising results of multimodality therapies, despite a definite lack of proof, have resulted in a widespread use of such regimens throughout the Western world. This attitude in part may be related to an outcome below standards of the surgical arm in a number of clinical trials. It seems therefore of paramount importance to optimise the surgical quality as a key to effective multimodality treatment.

A number of authors therefore have focused on the relation between outcome and hospital and surgeon volume as well as specialisation in achieving better surgical results. Although this debate is still open it seems that concentrating volume results in an increased incentive to set up detailed databases, more specific guidelines and protocols and regular multidisciplinary clinical conferences.

Concentrating patient volume will generate increased familiarity with the well known oncologic complexity of these cancers. More sophisticated facilities allow a more adequate staging e.g. by using PET scan, and thus avoiding unnecessary surgery. The particularities of the anatomy of the esophagus and the oncological principles governing the surgery require sufficient familiarity with different access routes, surgical techniques and accurate knowledge of pre- and postoperative management.

Whether lymphnode dissection is only diagnostic or indeed therapeutic is still an open question. But the role of adequate pathologic lymphnode staging in these tumours, particularly notorious for spread to nodes in the neck, thorax and abdomen despite tumour location versus the lack of accuracy of clinical staging of these nodes remains of paramount importance within the framework of multimodality regimens. As for many other cancers the effect of local recurrence on survival has been downplayed if not denied. Prevention of locoregional recurrence remains therefore an important goal in which quality of surgery plays a key role resulting in better cancer care in all respects.

In conclusion: striving for high surgical quality is an essential part of cancer care in general and for carcinoma of the esophagus and gastroesophageal junction in particular. Lack of surgical quality should never be a surrogate for the use of adjuvant therapeutic modalities. Therefore surgeons who care should assume a leadership role in defining the gold standard and best practice.

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Is quality control of radical prostatectomy feasible?

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Radical prostatectomy is performed by many urologists and the quality of the surgeon and the surgery itself should be optimal. The question is whether surgical quality can indeed be assessed.

We have made an attempt to evaluate the quality of the surgical act in a number of EORTC GU Group centers and showed that the duration of surgery, the blood loss, the postoperative continence, the margin positivity and the rate of undetectable PSA after surgery are highly variable and that this cannot be absolutely related to the caseload – as was shown in other cancer surgeries. A standard radical prostatectomy can be defined by a rather limited number of parameters that can even be collected retrospectively.