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 R 0 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 finding 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

T. Lerut. *U.Z. Gasthuisberg, Dept. Thoracic Surgery, Leuven, Belgium*

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?

H. van Poppel. *EORTC GU Group and University Hospital Leuven, Department of Urology, Leuven, Belgium*

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.

Large single center studies have been reporting their results on surgical, urological and oncological aspects of surgical treatment for prostate cancer. Single surgeon results have only been presented scarcely and then mostly reflect high quality and probably not the standard quality achieved in all centers.

The intersurgeon variability of surgical skill can be translated not only in peri- or postoperative complications but also in statistically significant differences as concerned to PSA progression.

Therefore it is clear that the surgeon who performs radical prostatectomy matters. The surgeon must inform his patients about his own outcomes and not about the results of high standard centers that have reported their experience. Indeed, there can be a relevant difference in morbidity and cancer cure.

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MLL gene rearranged leukemia: from biology to therapy

R. Pieters. *Sophia Children's Hospital, Ped. Oncology/hematology, Rotterdam, The Netherlands*

Childhood MLL gene rearranged acute lymphoblastic leukaemia (abbreviated as MLL) is characterised by a high incidence of a high white blood cell count, organomegaly, central nervous system involvement, myeloid features and the very immature CD10 negative precursor B-lineage phenotype. In vitro and in vivo mouse models showed that MLL grow better on stromal cell layers and are more resistant to cell death due to serum deprivation than other types of ALL. Most often MLL gene abnormalities reflect translocations; most frequent is the t(4;11) followed by t(11;19, t(9;11) and many other rare translocations. There are some data to suggest that > 1yr of age, the fusion partner is important for outcome: t(9;11) and t(4;11) do worse than others. The incidence of MLL is very high below 1 year of age (80%), and low in older children and at adult age the incidence is slightly increasing again. MLL has a relatively poor outcome with an EFS of 40% or less. Children > 1yr with MLL do better than infants < 1yr with MLL. Relapses occur relatively early; * occur within 1 year of diagnosis. This implies the need for intensive chemotherapy applied early. The benefit of allogenic stem cell transplantation in MLL is questionable and in a recent (not randomised) meta-analysis of MLL, survival in the transplanted t(4;11) group, especially those with an unrelated donor was not better than in the t(4;11) group receiving chemotherapy only. MLL shows a relative resistance in vitro and in vivo to glucocorticoids and L-asparaginase. However, MLL is in vitro significantly more sensitive to ara C and 2CdA than other types of ALL and AML, which can partly be due to a high expression of the nucleoside membrane transporter ENT1. Also clinical studies suggest that MLL benefits from treatment with HD-araC. Based upon these data, a large international collaborative treatment protocol (Interfant) has been designed that started in 1999. For future perspectives it is important that gene expression array analyses by independent groups have shown that MLL is characterised by a unique genetic profile, different from other genetic subtypes of ALL and AML. Of importance is also that by this genetic fingerprint genes may be identified that play a role in the leukemogenesis of MLL and that may serve as new therapeutic targets. Flt-3 is an example of this. Different studies showed that (wild type) flt-3 is significantly overexposed in MLL compared to other ALL and AML. In addition, inhibitors of flt-3 were shown to have specific activity in MLL cell lines, in a mouse model transfected with MLL and in patient samples from MLL cases, all these data compared to non-MLL ALL. This offers the opportunity to study flt-3 inhibitors in MLL.

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Risk adapted treatment for childhood ALL: the BFM experience

M. Schrappe[1], A. Schrauder[1], T. Flohr[2], C.R. Bartram[2], M. Zimmermann[1]. *[1]Med. Hochschule Hannover, Department of Paediatric Hematology/Oncology, Hannover, Germany; [2]University, Human Genetics, Heidelberg, Germany*

Close to 80% of pediatric patients with acute lymphoblastic leukemia (ALL) can be cured. To reduce the rate of relapses, but also to limit treatment morbidity, risk-adaption of treatment has been developed on the basis of extensive risk factor analysis. In addition to clinical factors (e.g. age, WBC), the immunphenotype and cytogenetic results, the early in vivo treatment response as determined by cytology had evolved as the most important predictor for relapse. Recently, the International BFM-Study-Group has demonstrated that standardized detection of MRD by identifying clone-specific T-cell receptor- (TCR) or immunglobuline (Ig) gene rearrangements can provide new, highly specific prognostic information. This allows to define three risk groups if BFM chemotherapy is being used (van Dongen et al., LANCET 352: 1731-38; 1998). Standard risk (SR): no evidence of MRD using two highly sensitive markers (sensitivity <=10-4) on day 33, and in week 12 before consolidation; medium risk (MR): MRD positive at d33 but low-positive (=10-3 at w12. For the new trial ALL-BFM 2000 refined logistics were developed to guarantee on-time MRD results. At least two independent Ig/TCR gene rearrangements had to be identified as PCR targets individually from the diagnostic material (bone marrow, BM). The two follow-up samples from week 5 and 12 (also BM) were analyzed quantitatively by real-time PCR (LightCycler). MRD results were reported to the participating hospitals via the study center 4-6 weeks later, after cross-checking with additional patient data relevant for stratification. More than 1200 eligible patients were enrolled since the start of the new trial. MRD-based stratification was possible in 81%. Based only on MRD results, 41% of the patients were eligible for SR, 50% for MR, and 9% for HR. When the additional risk group definitions (prednisone response, induction failure, translocation t9;22, or t4;11) were included according to protocol, all eligible patients could be stratified: SR comprised 33%, MR 52%, and HR 15% of the patients. In a randomized study with the AIEOP ALL group, postinduction treatment is reduced for SR, modified for MR, and intensified for HR patients. MRD-based stratification is feasible in a multicenter trial for childhood ALL if reliable logistics and lab methodology are available. Trial ALL-BFM 2000 is investigating whether this effort can be converted into a therapeutic benefit.

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Prognostic relevance of minimal residual disease in risk stratification of childhood ALL.

A. Biondi. *Ospedale Nuovo San Gerardo, M. Tettamanti Research Center, Monza, Italy*

The study of Minimal residual disease (MRD) as "surrogate" marker of molecular response to treatment, has drawn great interest because of the potential of tailoring treatment and the possibility of gaining insight into the nature of a cure. PCR-based MRD detection by Immunoglobulin (*Ig*) and T-cell receptor (*TCR*) gene rearrangements can be applied in more than 90% to 95% of childhood Acute Lymphoblastic Leukaemia (ALL) cases. Accordingly, several retrospective studies of MRD in childhood ALL have used one of the different PCR approaches for the detection of antigen-receptor gene rearrangements. The promising results on the predictivity of MRD evaluation at the end of induction treatment has challenged the need of a new definition of remission. Until now, most PCR-based MRD studies used semiquantitative methods for the detection of *Ig* and *TCR* gene rearrangements The introduction of Real-time Quantitative PCR (RQ-PCR) has resulted in the improvement of sensitivity, specificity and better quality control of the MRD data. Highly sensitive PCR techniques (detection limit $1x<10^{-4}$) allow the identification of a significant proportion of ALL cases with excellent clinical outcomes in the presence of negative MRD findings at early time points in treatment. By contrast, patients with 10^{-2} or more leukaemia cells during any phase of remission induction should be regarded as having a very high risk of relapse, thus becoming eligible for early transplantation or experimental treatment. How to use "intermediate" range of positive MRD findings ($>1x10^{-4}$ but $<1x10^{-2}$) is still unclear. Such patients might benefit from further intensification, but that possibility needs to be substantiated by randomised clinical studies. Thus, the German-Austrian BFM and Italian AIEOP study groups have adopted a MRD-based risk group classification for treatment stratification in their ongoing clinical studies. It is hoped that a more sensitive and specific evaluation of remission and early response to treatment could speed further improvement in cure rates for children with ALL.

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What is the best treatment for ALL in adolescents and young adults?

J. Nachman. *University of Chicago, Department of Pediatrics, Room C-408, Chicago, USA*

It is well known that adolescents with acute lymphoblastic leukemia (ALL) have a worse outcome compared to children 1-9 years of age. In a series of papers presenting results from recent pediatric ALL trials, event-free survival (EFS) ranged from 74-87% for children 1-9 and 55-70% for children > 10 years of age. The incidence of T-cell ALL is twice as high in adolescents compared to younger children. Restricting the analysis to patients with B-precursor ALL, patients >10 years of age have an increased incidence of common ALL antigen negativity, hemoglobin >11 grams, Philadelphia