Symposium (Mon, 24 Sep, 14:45−16:45)
Adjuvant treatment of colon cancer

30 INVITED

Open surgery for colorectal cancer – quality assurance

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The quality in the treatment of cancer has become more and more important. Based upon available data on colorectal cancer, the difference in cancer specific outcome between surgeons is larger than the beneficial effects of adjuvant chemotherapy. Therefore, it is important to know individual surgeons' outcome.
The only way to have knowledge about the outcome is of course a well organised quality control system. Once quality in surgical technique and surgical outcome has been registered, indicating that the standard of surgical care can be set, it is possible to continue with quality assurance.
In Sweden a quality control system for both rectal and colon cancer have been run for many years as a national registry for rectal and colon cancer. Data from the rectal cancer registry have been reported and evaluated based upon hospital. The difference between hospitals varies based upon number treated per year, i.e. volume. However, the difference in outcome between hospitals with different volumes is less than the difference between outcomes in high volume hospitals.
In conclusion, it is essential with a quality control system to see what standard of care we can expect in colorectal cancer treatment. Once those standards have been set, it is possible to continue with the quality assurance system.

31 INVITED

Five year results from the COST trial testing laparoscopic versus open colectomy for colon cancer

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Background: To test the hypothesis that disease-free and overall survival are not inferior regardless of whether patients receive laparoscopic-assisted (LAC) or open colectomy.
Methods: Sixty-six credentialed surgeons participated through one of 48 enrolling institutions. 5-year data was complete on 90% of patients. Because LAC was not under consideration as a superior oncologic procedure, a non-inferiority trial design was utilized testing time to recurrence as the primary endpoint. Additional endpoints included overall survival (OS) and disease-free survival (DFS) tested using Kaplan Meier.
Results: Patients with curable (TNM Stages I-III) colon cancer were randomly assigned to undergo LAC or open surgery; 872 patients were enrolled between 1994 and 2001 with a median follow-up of 7.15 years. Of 872 patients enrolled and followed until March of 2007, 252 have died and 170 patients have recurred. 5 year rates of cumulative incidence of recurrence (19% versus 22%), overall survival (77% versus 75%) and disease-free survival (69% versus 69%) are the same between the LAC and open arms, respectively. Sites of first recurrence were distributed similarly between arms. Recurrence rates, disease-free survival and overall survival did not differ by treatment arm based or TNM stage.
Conclusion: Results from a prospective randomized multicenter trial confirm that laparoscopic-assisted colectomy for curable colon cancer is not inferior to open surgery.

32 INVITED

Adjuvant treatment of stage II colon cancer

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Out of the million of patients (pts) world wide who have a colon cancer in 2007, approximately 20% will have a stage II colon cancer and for most of them the question of administration of an adjuvant treatment will be raised.
In contrast with the stage III for whom there a large consensus in favour of the administration of an adjuvant chemotherapy, using the FOLFOX 4 regimen in absence of counter-indications (Andre T et al. N Engl J Med 2004 and de Gramont A et al. ASCO 2007), there are still no consensus concerning the management of stage II colon cancer
The main reason for such incertitude is due to the fact that there is no large positive trial conducted in this specific population and because a low risk of relapse (15% to 30%) with a low risk of death (10% to 20%) results in a low potential absolute gain in overall survival (OS) estimated, for a HR of 0.80 in favour of chemotherapy, between 2 and 5%.
However 5 meta-analysis and two trials (QUASAR 2 and MOSAIC) give us some indirect arguments in favour of the efficacy of adjuvant chemotherapy using a 5FU based regimen for stage II colon cancer pts.
Two meta-analysis were borderline positive: the IMPACT B2 was a pooled analysis of 5 randomized trials (1016 pts) which reported an advantage of 2% (82% vs 80%) in favour of a 5FU and folinic acid combination but this difference was not significant (HR=0.86, p = 0.057) (IMPACT B2, J Clin Oncol 1999; 17: 1356−63); the Canadian meta-analysis conducted on 8 trials comparing surgery alone to surgery plus a 5FU based chemotherapy (1870 pts) also reported the same HR of 0.86 but also was not significant (p = 0.057) (Figueredo et al. J clin Oncol 2004; 22: 3495–3507).
Two meta-analysis were positive but the NSABP meta-analysis was a compilation of heterogeneous trials (Mamounas E et al. J Clin Oncol 1990; 17: 1349−55), and, the Japanese meta-analysis on 5233 pts was conducted in an heterogeneous group of pts with only 45% of stage II colon cancer for whom a + 4.3% increase in OS in favour of an oral 5FU based chemotherapy was reported (Sakamoto J et al. J Clin Oncol 2004; 22: 484−92). The last was a meta-analysis from the Mayo Clinic which was positive for the DFS (76% vs 72%; p = 0.049) but not for OS (81% vs 80%, NS) (Gill et al. J Clin Oncol 2004; 22: 1797–1806).
The QUASAR 2 study is the largest trial conducted in part in stage II colon cancer and compared, for pts with an uncertain benefit from chemotherapy, a group of pts treated by surgery alone (n=1617) to a group receiving a post-op 5FU and folinic acid combination (n=1622); it reported a significant difference for OS (5-year survival: 83% vs 80% in favour of chemotherapy, p = 0.04) however only two third of the pts had a stage II colon cancer and this trial has not been published (Gray R et al. Proc ASCO 2004; 24: Nº3501). In the MOSAIC trial approximately 40% of the pts had a stage II Colon cancer and these pts benefited from the same reduction in their relative risk of recurrence than the stage III colon cancer, however the DFS was not significantly ameliorated by the administration of the FOLFOX4 regimen compared to LV5FU2 (3-year DFS: 84.3% vs 87%; HR: 0.80 [IC95%: 0.56−1.15]) but the trial was not powered to answer questions on chemotherapy efficacy in stage II colon cancer (Andre T et al. N Engl J Med 2004).
In fact it appears from these studies that stage II colon cancer pts is an heterogeneous group of pts which must be separated into subgroups according to prognostic factors. For instance, in the large SEER cohort reported in 2004 there was an important difference in the OS of pts pT3N0 (stage IIa) (5-year OS: 83%) compared to pts with pT4N0 (stage IIb) (5-year OS: 72%) (O'Connell et al. J Natl Cancer inst 2004; 96: 1420−5).

- Since about 10 years a high risk subgroup of stage II colon cancer has been defined concerning pts with perorated or obstructive or pT4 tumors (Schrag D et al. J Clin Oncol 2002; 20: 3999–4005); other factors may also be considered like the existence of vascular invasion by the tumor, a poor tumor differentiation or a number of analysed lymph nodes <10 which are considered as poor prognostic factors (de Gramont et al. N Engl J Med 2004; 351: 1691−2; Moris M et al. Br J Surg 2006; 93: 866−71; Sarli et al Eur J Cancer 2005).
- Biological markers may also influence the risk of recurrence and for instance the MSS status is recognized as a factor of poor prognosis as well as the presence of a 18q LOH.

For pts having one of these poor prognostic factors and no counter-indication to receive chemotherapy there is an agreement to prescribe an adjuvant chemotherapy for high-risk pts who ask for it after extensive explanations on the benefit/risk ratio of the adjuvant chemotherapy (5FU-folinic acid combination or FOLFOX4 regimen).
In conclusion there is no consensus on the standard adjuvant treatment for stage II colon cancer pts. However in case of high risk of recurrences there is an agreement to propose an adjuvant chemotherapy to selected and informed patients. Ongoing trials will help us to precise the role of adjuvant chemotherapy in stage II colon cancer, in particular the ECOG E5202 trial which compares, in stage II MSS or 18q LOH, a chemotherapy (FOLFOX6) to a combination of this chemotherapy with bevacizumab.

33 INVITED

Adjuvant treatment of stage III colon cancer

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Background: The prognosis of patients with colon cancer depends on the depth of tumor invasion and whether regional lymph nodes are involved.

Patients with Lymph node positive disease are at high risk for tumor relaps and thus are potential candidates for adjuvant chemotherapy.
Materials and Methods: Publications of major journals and abstracts form major scientific meetings were reviewed.
Results: Several randomised trials comparing observation vs. 5-FU based treatment all reported that adjuvant chemotherapy results in an about 30% reduction of the risk of death and 6 months as compared to 12 months treatment duration are sufficient. Infusional 5-FU with leucovorin does not increase the results achieved with bolus 5-FU/FA but is less toxic. The oral fluoropyrimidines such as UFT/LV and capacitabine are alternatives to intravenous applications. The most promising data are reported with the use of capecitabine. Infusional 5-FU in combination with leucovorin and oxaliplation has further improved the efficacy by significantly prolonging the time to progression and as recently reported also the overall survival by about 4% in patients with stage III disease. The FOLFOX4 regimens is therefore the reference regimen and standard of care for this gorup of patients. Interestingly, the use of bolus 5-FU plus oxaliplatin (FLOX) confirms these results and indicates that oxaliplation is an important drug in the adjuvant setting. Long term neurotoxicity in about 12% of patients event after 4 years and in 75% within the first year has to be considered as a sequelae which ma ynot be acceptable for some patients. Irinotecan based regimens either with 5-FU given as a bolus or as an infusion have failed to improve over 5-FU/LV alone. Ongoing trials investigate the role of VEGF and EGFr antagonists.
Conclusions: Adjuvant chemotherapy should be offered to patients with stage III colon cancer. If FOLFOX4 can not be administered oral or intravenous fluoropyrimidies are second best options.

Symposium (Mon, 24 Sep, 14:45−16:50)
What is new in renal cancer

34 INVITED

An update on the molecular genetics of (hereditary) renal cancer: novel families, novel genes, novel diagnostic opportunities . . .

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Renal cell carcinomas (RCCs) represent ~90% of all primary renal tumors in adults. In recent years its incidence has been increasing worldwide. As yet there is no long term effective therapy for RCC, but if detected early and without metastases the tumors can be removed surgically. Such patients have a relatively good prognosis.
Besides sporadic RCCs also familial cases have been reported. Both share the presence of anomalies involving chromosome 3, suggesting a primary role for this chromosome in RCC development, particularly the clear cell type. Previously we, and others, have identified a number of families in which the occurrence of RCC co-segregates with constitutional chromosome 3 translocations. Based on allele-segregation, loss-of-heterozygosity and mutation analyses in these families, a multi-step RCC model was generated in which the occurrence of the chromosome 3 translocation acts as the primary step. Since then, this step-wise model was corroborated by several other investigators. As a corollary, we evaluated a cohort of ~100 Dutch families (Dutch Intergroup Study) known to segregate constitutional chromosome 3 translocations. Among these, several novel RCC families (as also families with other cancer syndromes) were detected. Additionally, we have collected an extensive series (~30) of RCC families without overt cytogenetic anomalies.
Aiming at the identification of additional RCC susceptibility genes, we initiated the positional cloning of the translocation breakpoints in these families. By doing so, we previously identified two novel genes, DIRC2 and DIRC3. Using similar approaches others identified FHIT, TRC8, DIRC1 and, more recently, LSAMP, NORE1 and TRC8. Interestingly, there appears to be a functional overlap between at least some of these genes. For the rapid mapping of additional familial chromosomal breakpoints and the identification of its corresponding genes, we developed a novel highly efficient microarray-based approach. In this approach chromosome flow sorting (FACS) and genomic microarray (arrayCGH) technologies have been integrated. In addition, we have developed a whole genome tiling-resolution BAC array (32K) for high-resolution detection of DNA copy number changes in cases lacking any apparent cytogenetic anomalies. Through the application of these array technologies we have been able to (i) precisely map novel translocation breakpoints and (ii) identify novel microdeletions/microduplications and their corresponding (onco-/tumor-suppressor) genes. Identification of these genes does not only provides us with relevant information for familial risk assessment, genetic counseling, and early detection, but also with clues with regard to alternative pathogenetic routes. Our ultimate goal is to establish an integrated model for (familial) RCC development, including the nature and role of its predisposing genes.

35 INVITED

Energy ablative therapy of renal cancer: new option or wrong track?

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Renal tumours <4 cm in diameter and detected incidentally in asymptomatic patients represent up to 50% of all solid renal lesions diagnosed today [1]. Although ~20% of them prove benign on histological examination and the majority grow slowly, 79% are renal cancers and of these 14% are multifocal, 15% Fuhrman grade 3−4, 22% >pT3a and 6% have metastasized at the time of diagnosis [2]. Nephron-sparing surgical excision is the standard therapy and achieves 10-year cancer-specific survival rates of up to 96%, with the rare recurrent tumour diagnosed after a median 5.4 years [3]).
Regardless of whether performed by open or laparoscopic partial nephrectomy, this carries a complication rate ~15% [4]. With the largest increase in incidence seen in the age group over 70 years of age with inherently high comorbidity, less invasive treatment options appear attractive. Based on small, retrospective series which suggest a low progressive rate, a watchful waiting strategy has been advocated for these tumours in infirm patients [5]. With at present no way to reliably identify the less aggressive tumours by imaging or percutaneous biopsy [6] and in view of the dominant histology of these tumours [2] this comes at considerable risk. Targeted destruction with less invasive energy based ablation appears safer. Small renal tumours are good targets, as they often have a spherical shape, are unifocal, located peripherally in the renal cortex and easy to locate by imaging. Ideally, the tumour is destroyed by an extracorporeal 'no touch' approach. The only non-radiation based technique theoretically capable of doing this is high-intensity focused ultrasound ablation. In clinical practice, problems with acoustic interphases from ribs and abdominal wall, ultrasonic inhomogeneity of the tumour and respiratory movement of the kidney have so far caused disappointing results with this technique, so that it remains strictly experimental at present [7]. Heating >60ºC causes instantaneous coagulative necrosis of all tissues, even in highly perfused organs like the kidney, and this is achieved by radiofrequency using either monopolar or bipolar electrodes. Under CT or MRI guidance, the electrodes can be placed percutaneously, even in local anaesthesia. Radiofrequency ablation's (RFA) main problems stem from the fact that tissue destruction cannot be visualised in real time, but has to be monitored by thermometry or changes in impedance. As a result, a recent metaanalysis of published data revealed a residual/recurrent tumour rate of 14% after percutaneous RFA of small, biopsy proven renal cell cancers, in spite of a mean follow-up of only <15 mos [8]. Even with state-of-the-art RFA equipment and technique and visual control of electrode placement, skipping of the area of necrosis and residual vital tissue has been demonstrated histologically after RFA ablation in 22% of tumours [9]. Skipping also seems to be the reason for late urinary fistula and ureteric strictures, which have been observed after percutaneous RFA [9].
After laparoscopic exposure of the kidney, cryoablation using needle cryoprobes and multiple freeze–thaw cycles under ultrasonic control has been utilised extensively. The objective is to freeze all tissues to be ablated below a minimum −20ºC [10], yet avoid all other structures. The ice ball, which is generated during the process, is not representative for this temperature, but can be monitored by laparoscopic ultrasonography. Clinical experience has shown that with an overlap of 6−10 mm beyond the tumour margin, reliable tumour destruction is achieved. With follow-up now reaching 5 years in some series, 92% of small peripheral tumours are completely ablated, as documented by a complete loss of contrast enhancement, progressive shrinking of the lesion and negative follow-up biopsies [8]. With the recent development of thinner cryoprobes ('cryoneedles') of 1.5 mm diameter and real time monitoring of needle placement and ice ball formation by open access, interventional MRI percutaneous cryoablation has come into the realm of clinical practice. Morbidity with the latter technique has proven low, but with retreatment needed in about 15% of tumours because of incomplete tumour destruction, results are still problematic [11, 12]. The keys to successful energy ablative therapy are correct patient selection and surgical technique, state-of-the-art technology and meticulous follow-up by serial cross-sectional imaging.
Patients with exophytic peripheral tumours <3 cm in diameter are ideal and complete ablation can be achieved in 95%, especially using laparoscopc cryoablation. Larger multifocal or central tumours have a high failure rate and a potentially significant complication rate, especially with RFA. Tumours on the anterior aspect of the kidney are difficult to reach percutaneously and the laparoscopic approach is definitely preferable. Complete loss of contrast enhancement and progressive shrinkage of the lesion on repeat CT or MRI studies are mandatory criteria for success. If this does not occur, follow-up biopsies are mandatory. If these guidelines are adhered to, energy ablative therapy definitely has a place in the management of renal cancer: it may be the therapy of choice in a high-risk surgical patient with a solitary, small and peripheral renal tumour. At this institution, using these criteria, 10% of 394 kidneys with tumours treated surgically 2002–