preservation of sexual potency. Previous trials have not demonstrated inferior survival in patients with T3 bladder cancer managed by radical radiotherapy reserving salvage cystectomy for those who recur. However, these trials have not been large. We have recently re-analysed the Institute of Urology trial which registered 189 patients between 1965 and 1976 to determine long-term results. The 5 year survival in 91 patients randomised to radical radiotherapy was 27.9% (19.1–37.8%). Whereas for 98 patients randomised to radiotherapy + cystectomy, the 5 year survival was 39.8% (30.3–49.8%). Since this trial, there have been advances in both radiotherapy and surgery. Conformal radiotherapy offers the potential for reducing radiation side-effects. Additionally, we have completed a study of accelerated fractionation treated to doses between 57.6 and 64 Gy in 32 fractions over 26 days. Eighty five patients were treated in this study and of 70 who had check cystoscopy at 3–6 months, a pathological complete response was seen in 80% with 2 further patients demonstrating carcinoma *in situ* only. We conclude that a trial is required based on modern staging and treatment techniques to compare radiotherapy and cystectomy for localised muscle invasive bladder cancer.

1001

## BLADDER CONSERVATION USING COMBINED EXTERNAL IRRADIATION AND IRIDIUM 192 IMPLANTATION

*L. Moonen*

*The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands*

For selected bladder carcinomas we consider iridium 192 implantation as the treatment of choice. Selection criteria that we use are:

1. Stages T1G3, T2 and T3a.
2. Solitary tumours.
3. Diameter not exceeding 5 cm.
4. No previous tumour elsewhere in the bladder.

From 1987 to 1994 63 patients have been treated. Results can be summarized as follows:

—Incidence of bladder recurrence at 5 years is 36%.

—About one half of the bladder relapses consist of secondary tumours.

—Isolated bladder relapses can be salvaged in the majority of the patients, many times with conservation of the bladder.

—Incidence of distant metastases at 5 years is 33%.

—In about one half of the cases distant metastases are combined with a bladder recurrence.

—Distant metastases are the major cause of death.

—Acute toxicity is limited and mainly related to the surgical procedure.

—Late toxicity is very limited.

1002

## NEOADJUVANT CHEMOTHERAPY AND ITS ROLE IN BLADDER CONSERVATION

*Mary K. Gospodarowicz*

*Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Canada*

Radiation therapy (RT) has been employed in the treatment of bladder cancer since the early 1900's, but its role in the curative management of bladder cancer is still controversial. Effects of RT are limited by cellular RT resistance, tolerance of normal tissues and the risk of systemic dissemination. Chemotherapy is active systemically, but few agents or combinations equal the antitumour activity of RT. The study of combined chemotherapy and RT is confounded by factors such as: specific tumour type, type of normal tissue involved, drugs selected, drug dosage and scheduling, RT dose, RT fractionation and overall treatment time and sequence of administration of each modality. Strategies for combining the two modalities include the use of drugs and RT concurrently, neoadjuvant chemotherapy or adjuvant chemotherapy. The first two approaches have been investigated in bladder cancer as CT delivered prior to or with RT also has the potential to improve local control beyond that achieved with RT alone. Current experience using concurrent and neoadjuvant chemotherapy in invasive bladder cancer will be reviewed with emphasis on the bladder conservation aspect of such management.

1003

## CHEMOTHERAPY AND RADIATION THERAPY WITH SELECTIVE ORGAN-SPARING TREATMENT OF INVASIVE BLADDER CANCER

*W.U. Shipley*

*Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, U.S.A.*

Several recent (1–4) reports supply new overall survival data for transurethral surgery and chemoradiotherapy as good as any reported cystectomy series which supports its safe and selective use for clinical stage T2–T3a patients. One likely important key to the improved success is the early identification of incomplete responders to chemoradiotherapy by prompt re-cystoscopy. This allows for prompt cystectomy before local regrowth (and a second chance for metastases) occurs.

| Series | Pts | 5 yr Overall Survival | 5 yr Survival with Bladder Preservation |
|---|---|---|---|
| Mass Gen Hosp (4) | 53 | 48% | 38% |
| U of Erlangen (1) | 197 | 45% | 36% |
| RTOG (4 yr data, 3) | 42 | 54% | 45% |

This multimodality and selective (by initial response) approach may, for stage T2–T3a patients, now become a standard treatment option in the US. Patients with tumor-associated hydronephrosis are not good candidates for bladder sparing.

1. Dunst J, Sauer R *et al. Int J Radiat Oncol 1994*,**30**,261.2. Housset M, Maulard C *et al. J Clin Oncol 1993*,**11**,2150.3. Tester W, Porter A *et al. Int J Radiat Oncol 1993*,**25**,783.4. Kaufman DS, Shipley WU *et al. N Engl J Med 1993*,**329**,1377.

1004

## RESECTION OF UNRESECTABLE HEPATIC METASTASES FROM COLORECTAL CANCER WITH NEOADJUVANT CHRONOTHERAPY

*H. Bismuth, R. Adam, C.H. Farabos, F. Levi*

*Hepatobiliary Surgery and Liver Transplant Center, Paul Brousse Hospital, Villejuif France*

In this study, we report a 6-year experience of the management of patients (pts) with hepatic metastases initially considered as unresectable and subsequently submitted to a resection following an efficient chemotherapy. From Apr. 1988 to Dec. 1994, 53 out of 330 pts (16%) with liver metastases initially considered unresectable underwent hepatic resection with a curative intent. All pts have been treated by intravenous chronomodulated chemotherapy combining 5 Fluorouracil, Folinic acid and Oxaliplatinum using an ambulatory programmable-in-time pump. Initial unresectability assessed by the same surgical team was related to large (n = 10), multinodular (n = 22), centrally located tumors (n = 8) or to the presence of extrahepatic disease (n = 13) with peritoneum (n = 6), epiploon (n = 3), lungs (n = 4). Pts received 3 to 29 courses of chemotherapy (mean = 9) for 2 to 21 months (mean = 7).

*Results:* An objective reduction of tumour size was observed following chemotherapy in all pts subsequently submitted to liver resection. A significant reduction of tumor markers was also demonstrated for CEA and CA 19-9. Mean follow up is currently 24 months for the whole group (range 4–68). Patient survival rate is 55% at 3 years similar to that of pts submitted to liver resection as a first treatment. Survival rate is higher in those 40 pts with technically unresectable lesions (large or multinodular or centrally-located) than in those 13 with extrahepatic disease, 58% vs 39% respectively.

*Conclusion:* A second-step resection may be achieved in some unresectable pts with the help of an efficient chemotherapy. The benefit in survival seems comparable to that obtained with liver resection as a first intent. This therapeutic strategy involves a multimodality approach including repeat hepatectomy and extrahepatic surgery.

1005

## NOVEL METHOD FOR DETECTING LIVER METASTASES

*T.G. Cooke*

*University Department of Surgery, Royal Infirmary, Glasgow G31 2ER, U.K.*

All patients undergoing curative surgery for colorectal cancer should have an accurate staging of their liver prior to treatment. However, conventional radiological methods which rely on the differences of density of neoplastic tissue and normal liver have limits in their resolution rarely detecting lesions less than 1 cm in diameter. An alternative approach is

to measure functional changes in the liver that result from the development of liver metastases. Over the last nine years, in a series of animal and clinical experiments, we have demonstrated that the presence of tumour within the liver causes changes in the hepatohaemodynamics with alterations both in hepatic arterial and portal flow. These changes appear to be the result of the release of a vasoactive agent although this has not yet been identified.

In patients hepatic and portal venous inflow can be measured indirectly using scintographic methods or more recently by direct measurements using colour Doppler flowmetry. Using both of these techniques, we are able to predict the development of liver metastases in patients undergoing curative colorectal surgery who have no metastases apparent at the time of surgery assessed by either computerised tomography or ultrasound techniques. These measurements independently predict prognosis for a patient and may be useful in selecting high risk cases for adjuvant chemotherapy.

1006
## PROGNOSTIC FACTORS INFLUENCING SURVIVAL AFTER SURGICAL TREATMENT

*L. Gennari, R. Doci, P. Bignami*
*Istituto Nazionale Tumori, Milan, Italy*

Liver metastases (LM) are still a main problem in oncology. While diagnosis is easily performed today, prevention and treatment are still difficult. Surgical approach can be technically performed in about 10% of the cases with LM. A classification should be used to evaluate results. Prognostic factors analysed are: primary stage, relapse time and preoperative CEA value, number and the site of M, surgery type, stage according to system we propose and in some cases cell biology of both primary and secondary tumours. No significant statistical differences are observed for sex, age, primary stage, surgery type and extent of liver involvement are important prognostic factors. Multivariate analysis was performed considering data primary stage, stage of M, surgery type and extent of liver involvement, the parameter where some significant $P$ value was observed. The main prognostic factor is primary stage followed by stage of liver disease.

1007
## NEW TRENDS IN THE TREATMENT OF LIVER METASTASES— REGIONAL CYTOSTATIC AND CYTOKINOTHERAPY

*L. Hafström*
*Department of Surgery, University Hospital, S-90185 Umeå, Sweden*

The concept of regional infusion or perfusion therapy of liver malignancies has been known for many years but has never gained wide acceptance—mainly due to lack of prospective randomized trials.

Recently one randomized study has identified a significantly prolonged survival for patients subjected to temporary hepatic artery occlusion followed by intraportal 5-fluorouracil and oral allopurinol compared to a no treatment group.

One "phase I" study has shown that isolated regional perfusion of the liver with hyperthermia and cytostatic drugs is feasible. An ongoing phase I study with a similar design plus TNF-$\alpha$ is under way. Preliminary results show an effect on sarcomas and melanomas.

More prospective studies evaluating regional therapy are warranted.

1008
## NEW SURGICAL AND COMBINED MODALITY APPROACHES TO COLORECTAL LIVER METASTASES

*P.M. Schlag*
*Virchow-Hospital, Humboldt-University Berlin, Robert-Rössle-Hospital, Lindenberger Weg 80, 13122 Berlin, Germany*

To improve the results of surgery in the treatment of liver metastases the following strategies are under investigation:

1. Adjuvant systemic and regional chemotherapy to eliminate micrometastases
2. Preoperative intraarterial chemotherapy to improve resectability and to avoid intraoperative tumour cell propagation
3. Intraoperative sonography as well to improve the definition of adequate resection margins as to detect additional metastases
4. Radio-Immuno-Guided Surgery (RIGS) or Laser-Induced-Fluorescence-Diagnosis (LIFD) to improve the intraoperative detection of micrometastases and of extrahepatic tumour manifestations
5. Laser-Induced-Hyperthermia (LIT) or cryotherapy to treat irresectable metastases
6. *In situ* or *ex situ* liver perfusion (work bench technique) to treat multiple liver metastases
7. Tumour cell vaccination to treat colorectal micrometastases

These strategies will have to be approved in further, carefully planned clinical investigations. There is hope that at least some of these concepts will add to a stepwise improvement of the results of surgical therapy in patients with colorectal liver metastases.

1009
## REGIONAL TREATMENT OF LIVER METASTASES BY EXTENSIVE SURGERY AND HIGH DOSE CHEMOTHERAPY

*C.J.H. van de Velde, A.L. Vahrmeyer, J.H. van Dierendonck*
*University Hospital Leiden, P.O. Box 9600, 2300 RC Leiden, The Netherlands*

Liver resection for colorectal liver metastases has changed dramatically in recent years. Better preoperative diagnosis and surgical techniques have improved the possibilities of this therapy with long-term survival and disease-free survival rates of 35 and 25% respectively. Also repeat liver resections can be performed with safety and good long term survival results. Unfortunately the majority of patients are not candidates for resection and systemic chemotherapy leads to responses in at the most 15% of patients. Hepatic arterial infusion has increased response rates but with few complete responses in the liver. We developed a recirculation perfusion of the vascularly isolated liver. At a dose of 3.0 mg/kg L-PAM was able to have a response in all patients with a considerable number of complete responses in this ongoing study. An update of the clinical results, the role of the tripeptide thiol glutathione (GSH) and future other applications of this technique will be presented. Clinicians should realize that in treating patients with liver metastases the only way to achieve survival benefit is to treat aggressively or not at all.

1010
## CONTROL OF INVASIVE CELL GROWTH BY RECEPTORS OF THE HGF FAMILY

*Paolo M. Comoglio*
*Institute for Cancer Research, University of Torino Medical School, Torino, Italy*

The HGF receptor family includes tyrosine kinases encoded by three oncogenes: *MET*, *Sea* and *RON*. The ability to promote uncontrolled proliferation represents only one of the two facets of their oncogenic potential. The three members of the HGF receptor family share a unique functional feature: they mediate cell motility in physiological conditions, and invasiveness in their activated versions. This suggests a role in tumorigenesis and in progression to the metastatic phenotype. The $p190^{MET}$ receptor is a heterodimer of two ($\alpha$ $\beta$) disulfide-linked protein subunits. Two receptor isoforms, carrying a native ligand binding domain but lacking the kinase domain, arise from alternative post-transcriptional processing. In physiological conditions, HGF binding triggers tyrosine autophosphorylation of its receptor, upregulating its kinase activity: site-directed mutagenesis of two tyrosine residues involved in the positive regulation of the catalytic activity ($Y^{1234}$ or $Y^{1235}$) strongly impairs the transforming potential of the oncogenic counterpart of the receptor. Negative regulation of the kinase activity occurs through distinct pathways involving protein kinase C or increase in the intracellular $Ca^{2+}$ concentration. Receptor autophosphorylation of a multifunctional docking site, made of the duplicated degenerate sequence YVH/NV, mediates interactions with multiple SH2-containing signalling molecules, including PI 3-kinase, phospholipase-C-$\gamma$, $pp60^{c-Src}$, and the GRB-2/SoS complex. Mutation of the two tyrosines ($Y^{1349}$ and $Y^{1356}$) of the bidentate docking site results in the abrogation of the transforming activity in the oncogenic counterpart of the receptor.

The *MET* oncogene is overexpressed (activated) in a significant fraction of human cancers, including thyroid and colorectal carcinomas. *MET* amplification is found in metastases. Cells transfected with the *MET* proto-oncogene display a motile and invasive phenotype in the presence of HGF. Recently we have identified the ligand for another member of the *MET* family, the *RON* receptor. We have shown that *Ron* is activated upon binding MSP (Macrophage Activating Protein), an HGF-like polypeptide involved in cell proliferation and chemotaxis.