expected from simple conformal radiotherapy in the treatment of pelvic tumours. *Radiother Oncol* 1988, **13**, 23–30.
5. Boesecke R, Doll J, Bauer B, Schlegel W, Pastyr O, Lorenz WJ. Treatment planning for conformation therapy using a multi-leaf collimator. *Strahlentherapie Onkologie* 1988, **164**, 151–154.
6. Matsuda T. Clinical significance of computer controlled conformation radiotherapy—from seven years experience. Proc. 8th ICCR, Toronto, 1984, 474–478.
7. Brahme A. Optimisation of stationary and moving beam radiation therapy techniques. *Radiother Oncol* 1988, **12**, 129–140.
8. Webb S. Optimisation of conformal radiotherapy dose distributions by simulated annealing. *Phys Med Biol* 1989, **34**, 1349–1370.
9. Kutcher GH, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. *Int J Radiat Oncol Biol Phys* 1989, **16**, 1623–1630.
10. Goitein M, Abrams M. Multi-dimensional treatment planning I(1). Delineation of anatomy. *Int J Radiat Oncol Biol Phys* 1983, **9**, 777–787.
11. Goitein M, Abrams M. Multi-dimensional treatment planning II. Beam's eye view, back projection and projection through CT sections. *Int J Radiat Oncol Biol Phys* 1983, **9**, 789–797.
12. Brahme A. Design principles and clinical possibilities with a new generation of radiation therapy equipment. *Acta Oncol* 1987, **26**, 403–412.
13. Podgorsak EB, Pike GB, Loivier A, Pla M, Souhami L. Radiosurgery with high-energy photon beams: a comparison among techniques. *Int J Radiat Oncol Biol Phys* 1989, **16**, 857–865.
14. Austin-Seymour M, Urie M, Munzenrider J *et al.* Considerations in fractionated proton radiation therapy: clinical potential and results. *Radiother Oncol* 1990, **17**, 29–35.
15. Slater JM, Diller DW, Archambeau JO. Development of a hospital-based proton beam treatment center. *Int J Radiat Oncol Biol Phys* 1988, **14**, 761–775.
16. van Herk M, Meertens H. A matrix ionisation chamber imaging device for on-line patient set-up verification during radiotherapy. *Radiother Oncol* 1988, **11**, 369–378.
17. Smith AR. Evaluation of new radiation oncology technology. *Int J Radiat Oncol Biol Phys* 1990, **18**, 701–703.

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Adjuvant Therapy for Colon and Rectal Cancer

NIH Consensus Development Conference

U. Metzger

INTRODUCTION

COLORECTAL CANCER is a major public health problem in Western industrialized countries. More than a quarter of a million people are newly affected each year. Over the past 30 years, the population-adjusted incidence has remained constant at 45–50 cases per 100,000, and thus the number of cases has increased due to population growth and increasing age. About three-quarters of patients with these cancers will have a primary surgical resection but, despite the high resectability rate and a general improvement in surgical therapy, nearly half of all patients with colorectal cancer die from metastatic tumour. Adjuvant therapy is administered in addition to resection. Options include chemotherapy, radiation therapy and immunotherapy. Over the past three decades, many studies have failed to demonstrate benefits from adjuvant therapy. Claims of efficacy have been viewed with scepticism. New data from several studies have demonstrated delays in recurrence and increases in survival for specific groups of patients.

Although the history of adjuvant therapy for colorectal cancer spans 30 years, only in the past 5–8 years have several trials yielded reproducible positive results. To evaluate this information and to resolve issues about adjuvant therapy for patients with colon and rectal cancer, the National Cancer Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a consensus development conference on 16–18 April 1990. After presentations by experts and discussion by the audience, a panel considered the evidence and agreed on answers to the following key questions.

WHO IS AT RISK FOR RECURRENCE?

Clarification of the role of adjuvant therapy for colon and rectal cancer and maximization of the benefit of adjuvant regimens require identification of those individuals most likely to develop recurrent disease. Patients should undergo evaluation of the remainder of the large bowel for synchronous lesions. The presence of inflammatory bowel disease, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer or more subtle familial associations should be assessed. Abdominal computed tomography (CT) or ultrasound for liver metastases should be done and carcinoembryonic antigen (CEA) should be measured preoperatively.

At laparotomy, complete surgical exploration is mandatory. Colon lesions should be resected with contiguous and regional lymph nodes. Adequate radial margins must be obtained to minimize local recurrence in rectal lesions. The pathologist should specify the gross and microscopic extent of all surgical margins, the depth of penetration, the number of nodes removed, the number involved and whether the apical node (highest level) is positive. The disease should be defined by TNM stage [1]. Characteristics such as venous or lymphatic invasion, perineural invasion, histological subtype and grade should be documented.

There are several possible prognostic factors in defining subgroups of patients at risk for recurrence. Pathological stage is the most important determinant of risk of recurrence. The degree of penetration of the primary lesion, the lymph-node involvement, and the number of involved nodes are all significant independent risk factors. There are differences in the natural history and patterns of failure between colon and rectal cancer that require the testing of distinct adjuvant strategies for lesions in the two sites. Elevation of preoperative CEA (over 5 ng/ml) indicates increased risk for recurrence. Raised CEA correlates with stage and histology. Normal preoperative CEA does not obviate the need for adjuvant therapy in node-positive patients. However, elevated CEA may indicate a high-risk subset with node-negative colon cancer. It is premature to use certain cellular or molecular characteristics as standard determinants of

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recurrence risk. Ploidy status and S-phase fraction are not consistently correlated with overall recurrence and survival. With refinement and standardization of the methodology, these factors may help to delineate stage II subsets at high risk for recurrence.

At a molecular level, mutation and losses of allele have been documented and may be critical in mechanisms of tumour progression. Several investigators suggest similar complexity of changes in gene expression and/or structure in colon and rectal cancer. Data from colorectal tumour cell lines that are characterized as poorly, moderately or well differentiated suggest that production and interaction of growth factors correlate with degree of differentiation. The clinical significance of these findings remains to be elucidated.

IS THERE EFFECTIVE ADJUVANT THERAPY FOR COLON CANCER?

Colon cancer tends to fail in the peritoneal cavity, the liver or in distant sites with only a small component of isolated local failure. Thus, systemic chemotherapy or immunotherapy is the optimum adjuvant. In the 1960s FUDR and 5-fluorouracil (5-FU) were given as adjuvants for varying periods postoperatively in a wide range of dosage schedules. Activity was demonstrable but not convincing statistically in individual trials. A meta-analysis [2] suggested some benefit with 5-FU. Levamisole plus 5-FU was first demonstrated as effective in 1987 [3]. The Mayo Clinic and the North Central Cancer Treatment Group (NCCTG) used this combination for stage II and III resectable colorectal cancer [4]. Quality control and analysis was excellent (median follow-up 7 years). The combination significantly reduced recurrence and subset analysis for stage III patients showed significant improvement in overall survival. An intergroup study of colon carcinoma was designed: patients with stage II disease were randomized to observation or to 5-FU plus levamisole and those with stage III disease were randomized to observation, levamisole alone or the combination. Median follow-up is 3 years [5]. Similar to an EORTC trial [6], levamisole alone had no significant effect. For stage III patients, 5-FU plus levamisole reduced the risk of cancer recurrence by 41% and overall mortality by 33%. There was no difference in outcome in stage II patients, but 1–2 years of additional observation is needed. Side-effects from this combination were well tolerated and primarily associated with 5-FU.

There are potential pitfalls in interpreting these results. The mechanism of action of levamisole is not understood and the positive results seen in the Mayo Clinic/NCCTG study were based on a small number of patients and a subset analysis. The short follow-up is a concern for the interpretation of results from the intergroup study.

Increased response rates have been observed in matastatic colon cancer with the use of 5-FU and leucovorin. This combination, with or without levamisole, is under investigation.

Recognition that the liver is the most common site of tumour recurrence has led to evaluation of portal vein infusion for adjuvant therapy in the regional control of hepatic metastases. Although some of these studies have reported significant improvement in disease-free survival and overall survival (presumed to be secondary to systemic effect), none, with the exception of the original study by Taylor *et al.* [7], have succeeded in reducing liver metastases. This form of therapy remains investigational. In view of the improved overall survival, other approaches for short peri-operative chemotherapy might be investigated.

IS THERE EFFECTIVE ADJUVANT THERAPY FOR RECTAL CANCER?

In contrast to colon cancer, there is a significant risk of symptomatic local-regional failure as the only or first site of recurrence in patients with curatively resected rectal cancer. The principal reason for local recurrence appears to be related to the anatomic constraints in obtaining wide radial margins. Over the past 10–15 years, adjuvant radiation therapy has been evaluated both preoperatively and postoperatively. Although local recurrence rates were significantly decreased, almost all studies showed no significant benefits in disease-free or overall survival.

In the first GITSG trial, the combination of 5-FU and methyl-CCNU with radiotherapy continues to show significant improvement in local control and survival (10 year follow-up) compared with surgery alone and somewhat better than either treatment on its own [8]. In the NCCTG study with a median follow-up of 6 years, the same combination was superior to radiotherapy alone [9]. In the NSABP study, a combination of 5-FU, methyl-CCNU and vincristine was significantly better than surgery alone but local failure (23%) remains high [10].

The best adjuvant therapy for rectal cancer is probably postoperative chemotherapy plus radiotherapy. The use of methyl-CCNU in most of the successful chemotherapy regimens is problematic in view of its demonstrated leukaemogenesis and nephrotoxicity. The panel was optimistic about the likely effectiveness of combined therapy, but recognized the need to study the effectiveness of combinations that do not include methyl-CCNU, such as 5-FU and leucovorin or levamisole or related combinations with radiotherapy for local control. Adjuvant therapy must be balanced against possible side-effects. Chronic radiation effects can be severe. Surgical attention should be directed to prevent small intestine loops from entering the pelvis, with either natural structures or synthetic mesh. Chemotherapy should be administered by skilled oncologists.

RECOMMENDATIONS FOR ADJUVANT THERAPY

Optimal adjuvant therapy for stage II and III colon cancer has not yet been devised and clinical trials are essential to discover more active therapies. Based on current data, stage III colon cancer patients unable to enter a clinical trial should be offered 5-FU and levamisole (administered as in the intergroup study) unless there are medical or psychosocial contraindications. The panel cannot recommend any specific adjuvant therapy for stage II colon cancer patients outside of clinical trials.

Combined postoperative chemotherapy and radiation therapy improves local control and survival in stage II and III rectal cancer patients and is recommended. The most effective combined regimen appears to be 5-FU plus methyl-CCNU and high-dose pelvic irradiation (45–55 Gy) but the chronic toxicity of methyl-CCNU militates against using this regimen outside ongoing clinical trials. Current clinical trials are designed to improve the prognosis of stage II and III rectal cancer patients and entry of patients into these trials is highly encouraged.

FUTURE RESEARCH

Major advances will require large, prospective randomized trials with well-balanced populations, and carefully stratified by known prognostic factors. There have been little biochemical or immunological data to support or reject the biological rationale on which to base trials. Future studies should incorporate laboratory studies of the principal underlying hypothesis.

Future trials should standardize 5-FU dose and schedule, and link these to some biological or biochemical end-point. The mechanism of action of levamisole needs investigation. Trials based on the results of the 5-FU/levamisole combination are hampered by the lack of data on the immunomodulatory effect, if any, or on the mechanism of action of the combination. This regimen is the standard with which new therapies should be compared. Other modulators of 5-FU, including leucovorin, interferon and PALA (N-(phosphonoacetyl)-L-aspartate), need study.

Adjuvant therapy is most conclusively established for patients with stage III disease. However, newer prognostic markers such as DNA content, proliferative activity, surface glycoprotein, gastrin receptor, oncogenes/tumour-suppressor genes and allelic deletions may allow the refinement of prognostic groups. Although local relapse is not common in colon cancer, there are certain groups (i.e., T_4, N_1/N_2) that have significant local failure rates and should be included in separate trials of radiotherapy combined with chemotherapy. Systemic adjuvant chemotherapy should be compared with direct portal infusion.

Since combined therapy can significantly reduce symptomatic local recurrence in rectal cancer, the next series of trials must define the proper dose, sequence and integration of these modalities. The impact on local recurrence and disease-free and overall survival must be measured against any increased toxicity inherent in the combined approach.

Quality of life and the cost-benefit ratio of adjuvant therapy should be investigated.

1. International Union Against Cancer. *TNM, Classification of Malignant Tumors*, Hermanek P, Sobin LH, eds. Berlin, Springer, 4th Edn. 1987.
2. Buyse M, Zeleniuch A, Chalmers TC. Adjuvant therapy of colorectal cancer. *JAMA* 1988, **259**, 3571–3578.
3. Windle R, Bell PRF, Shaw D. Five year results of a randomized trial of adjuvant 5-fluorouracil and levamisole in colorectal cancer. *Br J Surg* 1987, **74**, 569–572.
4. Laurie JA, Moertel CG, Fleming TR *et al.* For the North Central Cancer Treatment Group and the Mayo Clinic. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. *J Clin Oncol* 1989, 7, 1447–1456.
5. Moertel CG, Fleming TR, Macdonald JS *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990, **322**, 352–358.
6. Arnaud JP, Buyse M, Nordlinger B *et al.* Adjuvant therapy of poor prognosis colon cancer with levamisole: results of an EORTC double-blind randomized clinical trial. *Br J Surg* 1989, **76**, 284–289.
7. Taylor I, Machin D, Mullee M, Trotter G, Cooke T, West C. A randomized controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985, **72**, 359.
8. Douglass HO, Moertel CG, Mayer RJ *et al.* Survival after postoperative combination treatment of rectal cancer. *N Engl J Med* 1986, **315**, 1294–1295.
9. Krook J, Moertel CG, Wieand H *et al.* Radiation versus sequential chemotherapy–radiation–chemotherapy. A study of the North Central Cancer Treatment Group, Duke University and the Mayo Clinic. *Proc ASCO* 1986, 5, 82.
10. Fisher B, Wolmark N, Rockette HE *et al.* Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 1988, **80**, 21–29.

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Experimental and Clinical Status of Intraperitoneal Chemotherapy

Gerrit Los and J. Gordon McVie

INTRODUCTION

TRADITIONAL intravenous or oral therapy for cancers within the peritoneal cavity may soon give way to the anatomically more appropriate intraperitoneal route for adjuvant postsurgical or palliative treatment. The Second International Conference of Intracavitary Chemotherapy emphasized the important role of intraperitoneal chemotherapy in improving the complete remission rate of cancers restricted to the peritoneal cavity [1].

The peritoneal cavity is a common site of tumour recurrence after initial 'radical' surgical treatment of ovarian and various gastrointestinal malignancies. Dissemination in this cavity is often widespread. Because of the unusual natural course of ovarian cancer and low-grade gastrointestinal neoplasms, characterized by their tendency to be confined into the peritoneal cavity, control of metastatic disease in the peritoneal cavity is an important and challenging problem. During the past decade, a theoretical basis has been established from which the pharmacokinetics of drugs administered intraperitoneally can be predicted [2, 3]. Improved understanding of the principles of intraperitoneal chemotherapy has permitted the design of clinical trials which indicate that a large pharmacological advantage can be translated into improved survival. Further development of an effective therapeutic approach would have a major impact on survival of patients with ovarian cancer and might, to a lesser degree, improve survival in colorectal cancer. Our review describes the current knowledge of intraperitoneal chemotherapy and we point out the direction in which innovative treatments could be developed.

NATURAL HISTORY OF OVARIAN AND GASTROINTESTINAL MALIGNANCIES

Epithelial carcinomas account for 80–90% of ovarian malignancies. They appear to have a common origin, arising from the serosal mesothelial layer of the gonads. The most common mechanism of spread is by transperitoneal dissemination [4]. Table 1 shows the FIGO staging (the classification of the International Federation of Gynecology and Obstetrics) with 5 year survivals. Symptoms tend to appear late—only 25% of patients present in stage I or II [4].

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