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Management of Colorectal Cancer

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COLORECTAL carcinoma is the commonest visceral malignancy found in western countries. One may expect that every child born today in the western world has a 5% chance of developing colorectal cancer. Neither the incidence rate nor the survival rate of patients following surgical treatment have markedly improved in the past decades. However the knowledge of tumor biology and management of the disease is growing at a steady rate, with resulting definite improvements in the care of the patient with colorectal cancer. This knowledge has led to: (1) lowered mortality rates of surgical procedures as a result of improved perioperative management; (2) identification—of environmental carcinogens—of high risk patient groups—of patients at an early stage of the disease through screening studies; (3) adequate primary surgical treatments coupled with controlled clinical trials to test additional treatments; (4) careful follow-up after adequate staging of the disease with aggressive therapy for localized recurrent disease.

It is the purpose of this paper to concisely review concepts of surgical management of colorectal cancer with a critical analysis of the institutional experience with this disease.

EARLY DIAGNOSIS

Several facts suggest that survival from colorectal cancer would be significantly improved if adequate screening tests were to be generally employed. Apart from its common occurrence, its doubling time of about 600 days [1] allows ample time for detection. The improved prognosis one expects from cancer diagnosis in the asymptomatic state is apparently true for the Hemoccult method of testing [2]. Especially in identifying high risk groups, the use of colorectal cancer screening seems justified and a thorough work-up of patients with positive screening should be undertaken to find or exclude colorectal pathology. Once the diagnosis is established by barium (double contrast) enema and biopsy of the tumor by coloscopy a full set of laboratory data including liver function tests and a CEA baseline assay can be performed. Additional tests may be useful before proceeding with the surgical procedure.

MATTERS OF DEBATE IN SURGICAL TREATMENT

Cancer of the colon and rectum should be treated by wide resection of the tumor, including predictable areas of vascular and lymphatic drainage. Reconstruction and restoration of normal colonic function is proper to the surgical procedure. The main objective of the operation is the removal of the primary tumor and of any regional spread that may have occurred without allowing any further dissemination.

Why so many patients, especially with rectal tumors, and whose tumors have been completely and adequately excised, do eventually develop recurrence

Numerous studies have debated the '5 centimeter rule' in rectal cancer since intramural spread over more than 2 cm is exceptional and if so, only in poorly differentiated Dukes' C lesions responsible for widespread metastatic disease [3]. The routine application of the above rule may be against the patients' best interest (avoiding colostomy). High as opposed to low ligation of the inferior mesenteric artery has equally proved of no benefit for the patient [4]. Pararectal clearance may be more important [5]. The importance of lateral spread and consequences for the surgical procedure have been emphasized by Enker who favors a more extensive lymphatic resection [6]. In view of the poor prognosis for patients with lateral spread and due to the lack of a controlled study, the risks outweigh probably the benefits in routine practice. Prevention of implantation of potentially viable tumor cells by irrigation and occluding the bowel before mobilization, prophylactic oophorectomy in post-menopausal patients [7] and the use of the 'no-touch isolation technique' [8] are important surgical measures potentially valuable in individual patients with no additional risks. This latter technique is probably valid in cases with angio-invasive growth as shown in a recent clinical

trial [9]. The introduction of the 'stapling gun' has made it possible to restore continuity in patients with low rectal cancer, who 10 years ago would be doomed to live with a permanent colostomy. Whereas some studies indicate an increased risk of local recurrence due to less lateral radicality in anterior as opposed to abdominoperineal resection [10, 11], others could not find such a difference [12]. Provided the pelvic dissection is as wide as possible, the anorectal stump is irrigated with a cytotoxic agent, a distal clearance of at least 2 cm is obtained, and the upward dissection is as extensive in the AP resection, sphincter-saving resections should be equally as effective. Of course the only way of proving this hypothesis is to conduct a prospective randomized trial. Such a trial, however is unlikely to be performed as the problem of informed consent seems insurmountable. Apart from the above measures, the use of adjuvant radiotherapy appears to reduce the numbers of patients succumbing to the dreadful problem of local recurrence. Its relatively early occurence, usually within 2 years after operation implies that a considerable proportion of patients suffer from local recurrence before dying of distant disease. In 1975 and 1977 two clinical trials demonstrated an increase in survival due to pre-operative radiotherapy [13, 14]. A consecutive series of 42 patients from our institution treated by abdomino-perineal excision from 1975 to 1980 received pre-operative irradiation of 2000 rad. Our present follow-up data indicate that six patients developed a recurrence at an average of 17.5 months after surgery. Table 1 shows that local recurrences without distant metastases were only found in patients with Dukes' B tumors, whereas half of the local recurrences in patients with Dukes' B tumors were associated with disseminated disease. The patients with Dukes' A or D tumors did not benefit from the radiation therapy with a delay of surgery of usually 4 weeks. A recent randomized trial on 824 patients with operable rectal carcinoma compared surgery alone, 2000 rad in 10 daily fractions, and 500 rad as a single fraction, both given pre-operatively on survival and recurrence [15]. Unfortunately no difference was demonstrated in actuarial survival rates at 5 years. The local recurrence-free and metastasis-free rates were similar in all groups. The hypothesis that pre-operative irradiation by damaging tumor cells that would disseminate locally or distantly at the time of operation would improve prognosis, was not confirmed. There is however good reason to continue to explore the combination of surgery and postoperative radiotherapy in the management of patients with rectal cancer to determine their most effective clinical application measured by increased (local) recurrence-free survival. The optimum dose and technique however, have yet to be established and the rational selection of patients based on the stage of the tumor, confirmed.

Table 1. Site of recurrence and Dukes' classification in 42 patients with rectal carcinoma treated by abdominoperineal resection and preoperative radiotherapy

Site of recurrence		Dukes' classification			
		A	B	C	D
No recurrence	(59.5%)	5	18	2	–
Local only	(14.8%)	–	2	–	–
Local + distant	(9.5%)	–	2	2	–
Regional	(4.8%)	–	2	–	–
Distant	(21.4%)	–	2	4	3
Disease-free survival at 5 years: whole group)			62%	25%	(55%

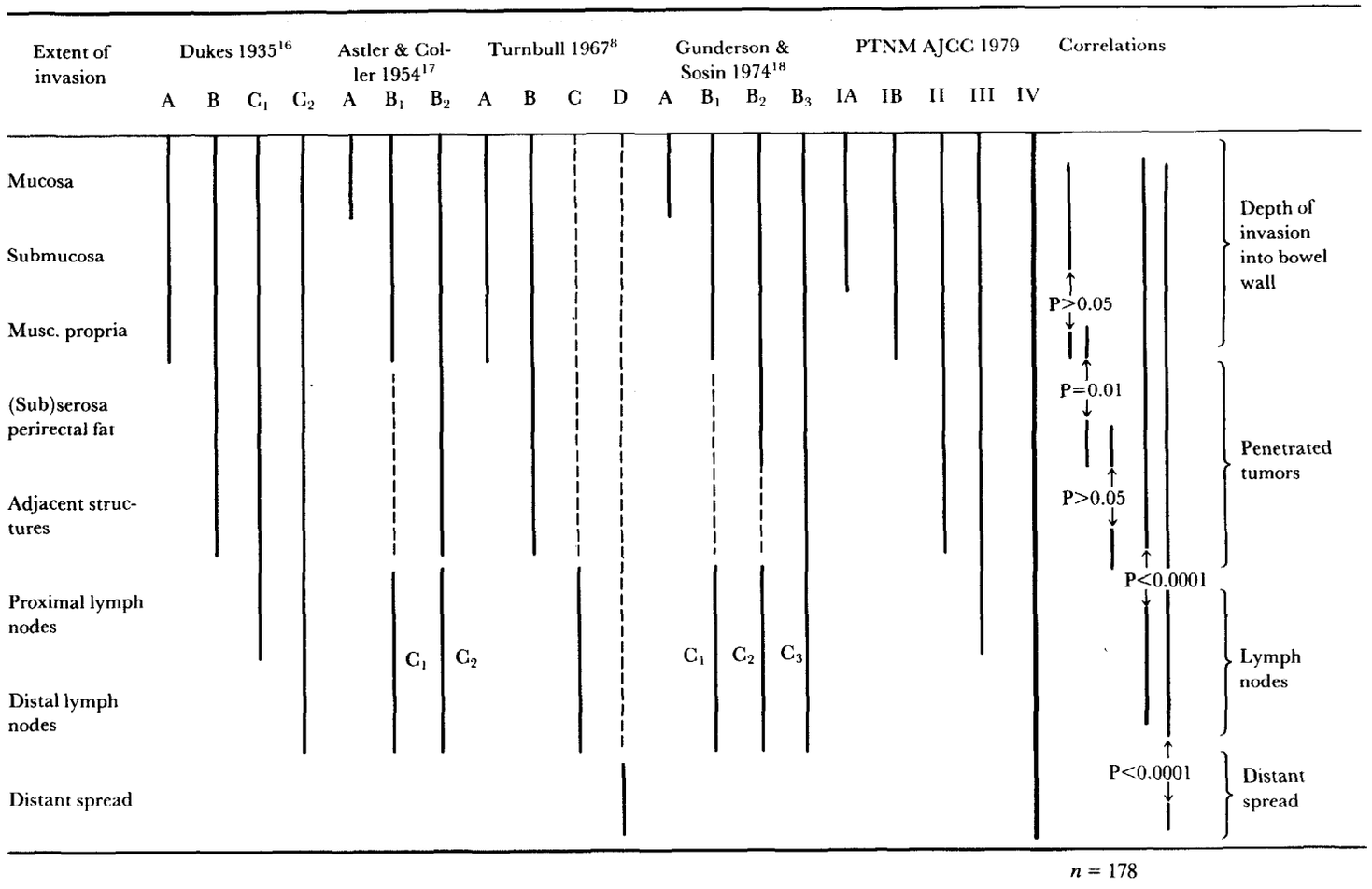
TUMOR STAGING

Perhaps the most confusing aspect of large bowel cancer is the staging of the disease. *With all the eponymous cancer classifications that have been presented in the past, have our prognostic ability and consequent therapies improved?*

Staging obviously should be clearly defined and be based on clinical and pathological criteria simple enough for everyday use. Significant differences should be found among subclassifications in prognostically homogeneous groups. Cuthbert Dukes performed pioneering work in both staging as well as in formulating his hypotheses concerning the spread of colorectal cancer. The Dukes' system [16] now often employed, is simple and easy to use, yet may fail to separate patients into prognostic groups adequately enough. In newer systems, complex classification of a patient becomes laborious and may be confusing. Table 2 presents some of the more commonly used staging systems. In a consecutive series of 178 patients from our department who underwent resection for colorectal cancer between 1966 and 1974 all histological slides were re-examined. The survival rates in the analysis and pairwise comparisons were corrected for death due to cancer only. Tumors confined to mucosa/submucosa ($n=11$) as compared to those confined to musc.propria ($n=32$) showed no difference in prognosis. A similar observation was made for tumors penetrating the serosa or into perirectal fat ($n=128$). The presence of lymph node metastases influenced the corrected 5-year survival rate significantly: 33% compared to 81% in the absence of nodal spread. The same was true for the presence of distant spread: 8-month median survival, whereas patients with no distant metastases had a 5-year survival of 72%. These data indicate that the A, B

Table 2. Staging systems for colorectal cancer

Staging system



and C categories of the original Dukes' classification are very valid. The effect of adding the D category proposed by Turnbull, markedly improved the survival statistics in the B and C categories by eliminating patients with a poor prognosis. With the lack of adequate systemic therapies, the simplicity and world wide use of the Dukes' classification favors its continued use.

ADJUVANT CHEMOTHERAPY

Even though chemotherapy appears to be, at best, of limited value in advanced colorectal cancer [19], there have been many efforts to apply this treatment at earlier stages of the disease as an adjuvant to surgery. Selection of cases for adjuvant chemotherapy is based upon the ability to determine the likelihood of relapse in patients who have undergone surgical therapy and have a relatively poor survival after intended curative surgery. Since liver metastasis is the most frequent site of distant recurrence, ongoing trials using liver-directed treatment (infusion, irradiation) should be followed with interest. The lack of proven efficacy and the side effects of these treatments [20] strongly favor the inclusion of a no-treatment control group in trials evaluating adjuvant treatment. It is probable that any future benefit of adjuvant chemotherapy in colorectal cancer will depend upon the development and testing of more potent and specific chemotherapeutic agents.

FOLLOW-UP

Careful follow-up of colorectal cancer patients after resection is important for several reasons: a second primary large bowel cancer will occur in 3–15% of patients; also, follow-up may in some instances detect recurrent disease when it is localized and amenable to further curative therapy. A prospective study attempting to determine the most sensitive objective test by which to detect recurrent disease showed that monthly CEA was the earliest indication of recurrence in 58% of patients [21]. Trends in serial CEA titers rather than isolated CEA values are currently employed in decision making to perform second-look surgery. This procedure is gaining interest and results indicate significant increased survival of reresected patients at the cost of a number of unnecessary explorative laparotomies [22]. The use of endoscopic follow-up seems very valuable both in detection of potentially resectable local recurrences in asymptomatic patients as well as to detect second primaries, as has been shown recently [23]. Our own data indicate if only routine biochemistry and physical examination is performed on a 3-month basis, half of our recurrent patients themselves make an appointment because of signs and symptoms of recurrent disease. No difference was observed when evaluating subsequent therapies in asymptomatic vs. symptomatic patients with recurrent disease detected by follow-up.

Continued periodic follow-up of patients after resection of a colorectal cancer has become a matter of tradition, with no careful analysis of the reasons for follow-up, what tests should be performed and what possible benefit the patient might obtain. A prospective randomized study comparing aggressive follow-up with yearly visits for physical examination in instructed patients, would give an answer to the cost/benefit ratio of early detection of recurrent disease.

HEPATIC METASTASES

Between 15 and 25% of patients with colorectal tumors have liver metastases at the time of initial presentation. In up to 30% of patients, the presence of liver metastases becomes apparent during follow-up. In a series of 69 patients from our department with unresectable liver metastases, survival time after diagnosis averaged 8.4 months independent of whether they were detected synchronously or metachronously. Liver resection is the only treatment available for colorectal metastases that has a significant chance of curing the patient. In reviewing the surgical literature on liver resection an average 5-year survival of almost 40% in selected cases is recorded [24]. The initial results of an inquiry on liver metastases treatment policies among 202 major hospitals from 12 western counties show some interesting results*. Follow-up was routinely performed in 98% of hospitals of which 84% used the CEA assay. Surgery for liver metastases was considered in the majority of hospitals (93.5%). The maximum resectability criteria in those hospitals considering surgery were: solitary lesions (30%), multiple lesions confined to one lobe (49%), multiple lesions in both lobes (21%). The majority of patients however present with unresectable metastatic disease. The results of the above mentioned inquiry showed that in only 29% of hospitals, patients with multiple unresectable lesions received no further chemotherapeutic treatment. Short term hepatic artery infusion chemotherapy with 5-Fluorouracil or its analogues results in an average of 12 months survival [25]. With the advent of many promising new treatment modalities like totally implanted devices for continuous drug infusion and isolated liver perfusion, and the lack of randomized trials including a no-treatment control group, the need for a universally used staging system becomes more important.

*To be presented by the author (C.J.H.V.) at the workshop for the design and implementation of adjuvant treatments following resection of hepatic metastases from colorectal cancer. National Cancer Institute, U.S.A., 9–10 May, 1985.

So far there is no uniform acceptance of any specific treatment for multiple liver metastases, since not one treatment has to date proved to be a real breakthrough. The lack of uniform reporting was noticed by Pettavel as early as 1967 when he proposed the Lausanne classification which was subsequently revised [26]. Surprisingly, surgery (= resectability), presently the only treatment available for colorectal metastases having any significant chance of curing the patient, is as yet not included in any staging system. In a proposed International Classification, (as a result of a workshop devoted to this problem [27]) based on the Lausanne classification the most important prognostic variables were included (Table 3). It should be noted that this staging system is not a dynamic one. It makes an assessment at a single point in time and has the advantage that it is simple enough, like the Dukes' system, for every day use.

Metastatic disease, in the majority of cases in the liver, usually represents the ultimate failure of our treatment of colorectal cancer patients. This multifactorial problem requires a co-operative approach to find useful answers.

Table 3. Proposed international staging system for hepatic metastases

Stage 0	: Curatively resected metastases
Stage I	: P_1 (PHR < 25%), no E, no S
Stage II	: P_2 (PHR 25–75%), no E, no S
Stage III	: P_3 (PHR > 75%), no S or any P with E and/or S
PHR	: Percent of hepatic replacement by tumor
E	: Concurrent extrahepatic disease
S	: Symptoms attributable to liver metastases

Selection of liver imaging technique to be made by each institution depending upon their expertise and available equipment.

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