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Staging and Surgery for Colorectal Cancer

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Staging of colorectal cancer has become increasingly important to select groups of patients for limited or more extensive surgery, and for adjuvant radiotherapy and chemotherapy. The main treatment is still surgery, but subgroups may benefit from adjuvant therapy, even accepting additional side effects. Accurate staging is necessary to define different treatment groups. A critical review is given of the present methods of clinicopathological staging.
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INTRODUCTION

STAGING AND surgical treatment of colorectal cancer (CRC) are interrelated procedures, resulting in a patient outcome, as expressed by risk of local and/or distant recurrence of the disease and chance of cancer-free survival or crude survival [1]. The outcome is also influenced by other types of treatment and possibly follow-up after treatment. Defining the stage is only meaningful when it makes it possible to state a prognosis and recommend the optimal treatment. Unfortunately, reproducible criteria of staging are not always available, making it difficult to compare different treatments in controlled trials; ultimately, the most accurate staging is not possible before the surgical specimen has been removed.

Many different systems of staging are in use. In 1988, recommendations for clinicopathological assessment and staging were published by the Colorectal Subcommittee of the United Kingdom Co-ordinating Committee on Cancer Research, dividing patients undergoing surgery into those having curative or non-curative operations, or operations which were indeterminate for cure [2]. In 1990, a critical review was given during the 9th World Congress of Gastroenterology by eight experienced workers in the field of CRC [3], concluding that it was necessary to establish an international terminology, which would make it possible to derive all staging systems according to the needs of clinicians and to exchange information between hospitals. Furthermore, it was foreseen that new prognostic factors might be identified in the near future, making it necessary to change the staging systems.

Several prognostic factors have already been identified, but others have not been generally accepted as having any importance. Increasing diagnostic efforts result in more cancers being detected at an early stage, making limited surgery attractive, but accurate staging is necessary to avoid insufficient, as well as too extensive, treatment.

The present paper is a short review of the criticism which has risen against the most common staging systems, but the review will also mention prognostic factors, which have not been fully evaluated. Staging will be discussed before as well as immediately after surgical treatment, but not during later follow-up and autopsy.

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DUKES' CLASSIFICATION

This system is used by most clinicians, but unfortunately the original staging [4] has been modified by several authors, and not uniformly. Dukes classified rectal tumours in those not penetrating the bowel wall and without lymph node metastases (A), those penetrating the wall, but still without lymph node metastases (B), and finally tumours with lymph node metastases, regardless of the depth of penetration of the cancer (C). Stage C was modified by Dukes in 1935 [5], dividing it in C_1 with lymph node metastases near to the rectal wall and C_2 with lymph node metastases near to the ligation of the superior rectal artery.

In 1949, Kirklin *et al.* [6] extended the use of Dukes' staging to include the colon, but it has been shown that prognosis may be different in the colon compared with the rectum in patients with the same Dukes' stage [7]. The authors [6] also changed the meaning of Dukes' A, now being limited to the mucosa, whereas B would mean penetrating into the mucosa, but not through the muscularis propria, and B_2 penetrating the bowel wall, including the serosal surface in colonic tumours. This change of definition in Dukes' stage A has caused much confusion, because it has been adapted in America but not by Europeans, who still prefer Dukes' A to mean cancers which do not penetrate through the muscularis propria. It must be emphasised that the definition of CRC includes penetration of the lamina muscularis mucosa, which has not always been pointed out in American literature [8] presenting tumours confined to the mucosa, not mentioning whether penetration of the muscularis mucosae has occurred; it is believed that tumours have to penetrate this layer before they are able to spread to lymph nodes. The conclusion has resulted in overtreatment as well as insufficient treatment; it is strongly recommended that tumours not penetrating the lamina muscularis mucosae should be called no more than adenomas with severe dysplasia, and words like carcinoma *in situ* and intramucosal carcinoma should be avoided [9].

In 1954, Astler-Coller [10] subdivided Dukes' C into C_1 meaning regional lymph node metastases, but tumour limited to the bowel wall, and C_2 when the tumour penetrated through the bowel wall with lymph node metastases; however, stage C_1 only presents a small part of all CRC [11]. In this context, it should be remembered that degree of invasion may vary in different parts of the tumour making it mandatory to look at several sections before deciding whether the muscularis propria

has been penetrated [12]. Unfortunately, the authors did not add anything to solving the problem of obtaining a uniform terminology for Dukes' stage A.

The previous stagings were based on examination of resected bowel and adjacent mesentery. In 1967, Turnbull *et al.* [13] introduced a clinicopathological staging which has achieved worldwide use; he adapted the staging by Dukes [4], but added a stage D, meaning metastases to distant organs; patients with unresectable tumours because of parietal invasion or invasion of neighbouring organs were also placed in stage D. Again, most Europeans have not used the last distinction, but usually they mention whether Dukes' B or C tumour have invaded the abdominal wall or other organs.

During the past two decades overall 5-year survival figures after surgery alone have been 70–83% for Dukes' A, 48–62% for Dukes' B and 22–33% for Dukes' C, using the original classification, but within the rectum as well as colon [14–17]. The corresponding figures for cancer-free survival have been 82–92%, 64–78% and 35–60%, respectively [7, 14, 15, 17]. It must be realised that survival figures may vary, depending upon the thoroughness with which the pathologist looks for penetration of the bowel wall and lymph node metastases. Also, 5-year survival is sometimes reported after exclusion of immediate postoperative mortality [14].

The large variations in survival figures suggest that Dukes' staging is unreliable; however, it is the simplest method today, and it is questionable whether prognostic discrimination will improve by using the TNM system, unless clinical and other than pathological variables are included in the staging procedure [18, 19].

TNM CLASSIFICAITON

The International Union Against Cancer (UICC) proposed a clinical classification in 1966, separating colonic and rectal cancer [18]. However, the proposition was withdrawn and tumours were then classified by extent of primary tumour (T), condition of regional lymph nodes (N) and presence or absense of distant metastases (M) at time of diagnosis, including a pretreatment clinical classification (TNM) as well as a postsurgical histopathological classification (pTNM) [20, 21]. A further modification was made, including a residual tumour classification (R), following recommendations by UICC and the American Joint Committee on Cancer (AJCC) in 1987 [3].

The use of T_{is} (carcinoma *in situ*) and pT_1 (intramucosal carcinoma) has been dissuaded by some authors, because of no potential for metastases being present [22, 23]. Also, there is no agreement upon whether infiltration beyond the muscularis propria in areas devoid of serosa should be classified as pT_2 or pT_3 [23]. Patients with extrarectal invasion without lymph node metastases have a worse prognosis than those with penetration of the muscularis propria only [24]. Other unclear definitions are present within pTNM, making it less than optimal as an international staging system [23].

Additional prognostic factors are of importance within some of the pTNM stages and not within others; multivariate analyses have shown no influence on survival of well-known prognostic factors like histological type, grade and venous invasion in some of the substages [25].

Distant metastases as defined within the TNM classification are traditionally demonstrated by clinical examination, chest X-ray (tomography), ultrasound of the liver with biopsy of suspicious lesions and possibly computed tomography of the abdomen as well as the chest. More recently, radioimmunological techniques have been developed, but sensitivity and specificity varies, and so far they cannot be recommended for routine use in the clinic [26–30]. During surgery, the number of liver metastases in both lobes and tumour burden should be estimated, ideally by use of ultrasound. Other residual tumours should also be documented, since both findings are important for later surgery for metastases and may even be decisive for initial portal infusion chemotherapy [31].

ACPS CLASSIFICATION

The Australian Clinico-Pathological Staging System (ACPS) is based on much information and allows staging, whether the tumour is treated or not [32]. Clinical, radiological, surgical and pathological informations are used, and the clinicopathological stage [A: not beyond muscularis propria, B: beyond muscularis propria, C: lymph node metastases, D: local tumour remaining (histological) or distant metastases (clinical or histological)] has been shown in a prospective study to have a stronger association with survival than the classic Dukes' system, the Astler-Coller modification [33] and other prognostic factors like grade, direct spread, venous invasion, age and sex, and colonic obstruction [34].

The pTNM classification may not achieve the same accuracy as ACPS, when separating the patients in different groups of survival [35] and the pTNM system is more difficult to memorise. However, stage A, B and C within ACPS may include subgroups with different prognoses [36].

CLINICOPATHOLOGICAL PROGNOSTIC FACTORS

Age

It has been suggested that CRC in the young may have a poor prognosis [37, 38], but others have found no relationship between prognosis and age [39–42]. Advanced CRC may occur more often in patients aged less than 40 years old, and poorly differentiated tumours as well as mucinous and signet cell carcinomas may be more frequent [37, 38, 43]; however, most studies suggest that a poor prognosis is related to stage of the disease at diagnosis and not to a more aggressive type of tumour [39, 40, 44].

Increased age is generally believed to be associated with a shorter survival after diagnosis of CRC. Age itself is probably of minor importance [45–47] compared with severe complicating diseases resulting in an increased postoperative morbidity and mortality [47–49] and therefore decreased long-term crude survival. Stage distribution seems to be similar to that in younger age groups [47, 50], but selection bias may be present, because the general practitioner does not always refer elderly patients with an advanced stage to hospital [46].

Sex and race

Women seem to have a better prognosis than men [51, 52] and parity also is associated with a longer survival than nulliparity [51]. Caucasians have a better prognosis than blacks and this discrimination is significant in univariate as well as multivariate analysis of a number of other independent prognostic factors [53].

Site of tumour

Site of tumour has been shown to be an independent prognostic factor [54–56]; a decrease in survival has been found when moving from the right colon to the left colon and rectum [17, 56]; others have found the shortest survival in patients with tumours in the left colonic flexure [55]. In some studies [54, 57]

patients surviving radical surgery for Dukes' B and C colorectal carcinomas have a better prognosis for tumours in the left colon compared with those in the rectosigmoid and rectum, but not in others. The prognosis is worse in the lower part of the rectum [45, 59, 60].

Size of tumour

Size of tumour has questionable independent prognostic significance [61, 62]; it has been shown not to be related to regional lymph node involvement, when measuring diameter and comparing Dukes' B and C cancers [63]. However, the tumour volume has been found to be larger in Dukes' B cancers of the rectum [64], supporting the old assumption that small tumours are the most malignant. A patient with a 10-cm exophytic tumour may have a better prognosis than a patient with a 5-cm non-exophytic lesion [62]. On the other hand, the number of quadrants involved in the rectum predicts the possibility of curative resection, being less when more quadrants are affected [45, 65]; this may to some degree be explained by the relationship between size and mobility of rectal tumours [65]. In Dukes' C cancers of the rectum and rectosigmoid, increasing size led to a worse prognosis as estimated in a multivariate analysis [60]. In another study [57], in which no distinction was made between colonic and rectal cancer, tumours 0–3 cm in diameter were followed by a longer disease-free survival than those greater than 3 cm.

Tumour mobility

Tumour mobility is of prognostic value when evaluated during digital rectal exploration or during surgery [45, 66–69], 5-year survival being decreased two to four fold, when the tumour is not mobile [70]. The prognosis in tethered tumours is nearly the same as for completely fixed tumours in the rectum [45]. However, when rectal tumours are tethered by inflammation only, they may have the same prognosis as mobile tumours, provided they are similar according to the presence of other prognostic factors [68].

Invasion of neighbouring organs

Invasion of neighbouring organs, confirmed by histological examination, is associated with a poor prognosis [71, 72], which may to some degree be explained by more frequent lymph node metastases [60, 73] and more poorly differentiated tumours [71]. This knowledge should not result in separation of adherent organs instead of *én bloc* resection, the latter having a better prognosis [74]. Forty per cent of the patients thought to have invasion of neighbouring organs, as evaluated by the surgeon, may only have inflammatory adhesions [73,75], and should certainly not be considered incurable. Malignant fistulas between the rectum and the genital tract may be followed by 30–50% 5-year survival when treated by radiotherapy and *én bloc* resection [76]. When surgery consists of no more than cutting the adhesions to neighbouring organs, the 5-year survival may be zero in those with a histologically confirmed invasion [77], stressing the need of more aggressive surgery [78].

In the rectum, endoluminal ultrasound examination may be superior to digital examination in detecting whether the tumour has invaded perirectal fat and/or neighbouring organs [79–82], whereas computerised tomography and magnetic resonance imaging (MRI) are less helpful [83, 84]; however, the method of MRI has not been worked out finally [85].

Acute intestinal obstruction

Acute intestinal obstruction indicates a poor prognosis, partly due to immediate postoperative complications [86–88] and partly due to a more advanced stage of the disease than in non-obstructing tumours [58, 88, 89]. Obstruction is seldom in the right colon and the rectum, but most frequently in the sigmoid colon, followed by the left flexure [90]. The majority of patients are above 70 years old [87].

Tumour perforation

Tumour perforation is associated with early recurrence and a poor prognosis even after adjusting for Dukes' stage [58, 91]. The prognostic ability seems to be much higher than that of acute obstruction [58], but long-term survival may be the same in patients with acute obstruction associated with tumour perforation or no perforation. Inadvertent intraoperative perforation of the tumour also increases the risk of local recurrence and carries a poor prognosis [92].

Resection margins

Resection margins of at least 2 cm below the macroscopical appearance of a rectal tumour have been considered adequate during the past decade [93–96], but most recently it has become evident that adequate lateral resection margins are of major importance if risk of local recurrence shall be kept to a minimum [97]. Lateral spread may be underestimated by the surgeon as well as the pathologist and may explain the large variation in risk of local recurrence from one surgeon to another [11]; it may be as high as 75% if lateral margins are invaded [98]. However, it is not quite clear whether mesorectal spread is related to the presence of lymph node metastases [99], which seems to be the case with distal intramural spread [100]. The presence of abnormal quantities of sialomycin at one or the other resection margin may increase the risk of local recurrence and a poor prognosis in patients with CRC [101].

Tumour differentiation.

The original classification of Broders [102] divided tumours into four groups, depending on how large a part of the tumour presented with poor differentiation. Unfortunately, criteria of differentiation are subjected to large inter- and intra-observer variations [103], but poorly differentiated tumours usually have a worse prognosis than moderately and well-differentiated tumours [104, 105]. It has been recommended that only poorly differentiated tumours should be defined, reducing the variability of observations [106]. The presence of a mucinous tumour component probably has no prognostic value when adjusting for stage and degree of differentiation, unless it is a signet cell carcinoma [107]. Nuclear shape as determined by morphometry may have an independent prognostic significance [108].

Lymph node metastases

The number of these may have the strongest prognostic value, when compared with the level of lymph node metastases and depth of tumour invasion in Dukes' C tumours [109]; it is possible to separate a subgroup, not penetrating the bowel wall, with one to four positive nodes, which has a similar prognosis as some tumours classified as Dukes' B [110]. However, the number of nodes detected depends upon surgical technique as well as the skill of the pathologist [111, 112], and it has been demonstrated that survival increases when the number of removed uninvolved nodes increases in patients without positive nodes [113]. On the other hand, high ligation of the inferior

mesenteric artery has not been found to improve 5-year survival in rectal and sigmoid cancer [114], and survival is the same after left hemicolectomy and segmental colectomy [115] and has not been proven to be prolonged by extended abdomino-iliac lymphadenectomy in rectal cancer [116, 117].

Immunohistochemical detection of carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA) expression using indirect immunoperoxidase staining method has not increased the number of positive nodes and will, therefore, not change the stage [118]. The optimal dichotomisation seems to be between one and three and four or more positive nodes, the latter reducing 5-year survival from 66 to 37% in patients with colonic cancer [119]. The knowledge about prognostic ability of number of lymph node metastases in tumours not penetrating the bowel wall is incomplete [110, 120].

Venous and neural invasion

Detection of tumour cells in the peripheral blood as well as lymphatic capillaries has no prognostic value [121, 122], whereas invasion of veins, especially thick-walled extramural veins, is tantamount to increased risk of liver metastases [60, 123, 124]. The influence on prognosis is independent of Dukes' stage [125] and of number of positive lymph nodes. Invasion of intramural veins alone has no prognostic value [126]; this has been confirmed in patients with malignant colorectal polyps, in whom it is found in 25–50% of cases [127]. Invasion of veins may be quantitated and a more detailed prognostic selection may be obtained [128].

Invasion of lymphatic vessels also has an independent prognostic value [129] and is seen more frequently in patients with venous invasion; incidence and number of positive nodes is also increased when lymphatic vessels are invaded.

Extramural neural invasion has an independent prognostic value [60, 124, 130] and is nearly as frequent as venous invasion. The local recurrence-free 5-year survival decreased from 81 to 64%, when neural invasion was demonstrated in specimens with rectal cancer [131].

Lymphocytic infiltration, tubule configuration and pattern of growth

These were evaluated in a Cox model for rectal cancer by Jass and coworkers and were allowed to compete with stage-related parameters in an overall model of pathological prognostic categories [132]; the parameters selected in the best model were number of positive lymph nodes, presence of lymphocytic infiltration and extent of spread through the bowel wall, resulting in five prognostic categories. Corrected 5-years survival decreased from 92 to 36%, when moving from pronounced to little lymphocytic infiltration [133]. In 1987, a new pathological classification, therefore, was suggested, based on number of positive nodes, extent of bowel wall invasion, character of invasive margin and peritumoral lymphocytic infiltration, which was claimed to place twice as many patients into groups that provided a confident prediction of clinical outcome after radical surgery for rectal cancer [134]; typing of rectal cancer as mucinous, non-mucinous and signet all gave no additional prognostic information [135], and the same was true for venous invasion.

Unfortunately, a Cox analysis provided another prognostic model for colonic cancer, even if it was superior to that of Dukes' [136]; preliminary evaluation of the Jass classification in another small study [137] suggests that it is too early to recommend it for routine use.

Synchronous colorectal neoplasia

Two or more cancers are present in 5% of the patients [138] and 25–35% have synchronous adenomas [139]. Both groups are generally believed to have an increased risk of metachronous colorectal cancer [140], but this might not be true when colonoscopic follow-up with polypectomy is instituted [141]. Synchronous carcinomas are more frequent when synchronous adenomas are present [138], and the prognosis seems to be no worse in patients with synchronous carcinomas compared with those with a single CRC [142, 143].

There is some evidence that patients with synchronous adenomas, regardless of Dukes' stage, may have a better prognosis than those without [139, 140], but this possible prognostic factor has not been fully evaluated in multivariate analysis [136]. Carcinomas with synchronous adenomas may have a lower incidence of DNA aneuploidy than CRC in general [144]. The prognostic value of adenomatous remnants within a carcinoma is not certain, but a high frequency has been found when the tumour is limited to the submucosa, is well differentiated and has an exophytic growth [145]. Adenomatous remnants are also present more often with synchronous adenomas [145].

Hereditary non-polyposis colorectal cancer does not seem to have a worse prognosis than sporadic CRC [146, 147]; it is more frequent in the right colon and at a younger age, and is more frequently accompanied by synchronous neoplasia in the colon and rectum and other organs.

Laboratory techniques

Tumour DNA content can be measured by flow cytometry, but it is doubtful whether aneuploidy will have any clinical importance as an adverse prognostic factor, in spite of being defined so in several regression analyses [148–152] and in spite of measurements being possible from surgical biopsy specimens [153]. The proportion of tumour cells in the S-phase may be as important a prognostic factor as aneuploidy, but reproducibility of this measurement is poor [154].

Preoperative measurements of serum carcinoembryonic antigen (se-CEA) are of prognostic value [155–158]. No reduction in postoperative values suggests that residual tumour is present [155, 159, 160], but normal values do not exclude this [155]. Marked elevation usually indicates distant metastases [157, 161]. Preoperative se-CEA levels represent an independent prognostic factor in patients with resectable CRC Dukes' C and sometimes Dukes' B [60, 156, 158, 162–164], but the levels are raised in no more than 40–70% of all patients with CRC [165] and CEA is less frequently expressed by poorly differentiated tumours [166]. Se-CEA has been found to be elevated more often in patients with DNA-aneuploid tumours and to correlate with stage in these [167].

Other tumour associated antigens have shown no or questionable advantages to CEA [168], when the latter has been measured in serum or tissue [169, 170]. A simple estimation of erythrocyte sedimentation rate or leucocyte count may be as effective as measurements of CEA [171], but this has not been studied in major investigations, so far [172]. Also, certain peptidases and other tissue and serum enzymes show elevation in patients with CRC [173–175], and they may have prognostic value.

Measurement of serum alkaline phosphatase has some prognostic ability in connection with Dukes' stage and sex, predicting the risk of later liver metastases [176].

Epidermal growth factor receptors have been demonstrated in CRC, and high values are associated with a poor prognosis [177].

Evaluation of the level of *ras*-gene protein product (p 21) in colorectal cancers suggests that an overproduction may be important for the later development of distant metastases [178].

SURGERY AND OTHER TREATMENTS

Many technical aspects have been revised during the past decade. The value of no-touch technique is uncertain, but still is subjected to the benefit of doubt [179]; sphincter saving resections for rectal cancer have considerably diminished the number of abdominoperineal excisions without any accompanying decrease in survival [180]. The number of blood transfusions during surgery has been reduced as well as plasma infusions, but it is doubtful whether transfusions influence long-term survival [181], in spite of a possible suppression of the immune response to CRC.

The main treatment for CRC is still surgery, but options are available, including adjuvant radiotherapy and chemotherapy. In some countries preoperative radiotherapy has been used in patients with rectal cancer, but it has not always been possible to demonstrate any effect on risk of local recurrence and seldom an effect upon survival. This may to some degree be explained by the difficulties in staging rectal cancer before surgery; progress has been made in detecting the depth of invasion, but it is, seldom possible to decide whether lymph node metastases are present or not. The regional lymph nodes may be removed to various degrees of completeness by different surgeons and it is, therefore, not surprising that risk of local recurrence varies from 3 to 40% without adjuvant radiotherapy. The latter, which is not without side-effects, should be given to those patients in whom the positive nodes cannot be removed by the surgeon, but not to compensate for poor surgery. Ideally, surgeons should be evaluated in the Cox model used for weighting of different prognostic factors, but it becomes increasingly difficult with increasing number of surgeons with different capabilities. Also, evaluation of the surgeon would mean doing a prospective study, a policy which is known to result in better prognosis itself, and no difference may be demonstrated between surgeons from university centres and community hospitals[182] under these circumstances.

Radiotherapy alone may change the Dukes' stage [183]; Broders' grading became unreliable in a recent randomised study, using a dose of 20 Gy in 4 days before surgery [184]. On the other hand, applying 45–56 Gy and 5-fluorouracil as a sensitiser preoperatively demonstrated no down staging in Dukes' classification in a recent study of 23 patients with rather advanced tumours [185]; retrieval of positive lymph nodes was nearly the same as in non-irradiated patients, but a marked reduction of tumour mass resulted.

Preoperative overstaging cannot always be avoided, especially when evaluation is done by digital rectal exploration. Endoluminal ultrasound of the rectum becomes increasingly important when more early cancers detected by screening [186] are removed by local surgery or even endoscopical polypectomy. In this context, it should be remembered that most studies on staging of CRC have been performed in symptomatic patients, making it possible that this staging may be inadequate in a screening population.

At the other end of the spectrum, bowel obstruction is not always defined according to strict criteria, making it difficult to evaluate the prognostic importance; only studies of emergency cases should be considered—the criteria of tumour perforation are less susceptible to criticism.

The rationale of postoperative radiotherapy in rectal cancer has been the better possibility of selecting the proper stage; endoluminal ultrasound examinations may partly change this and thereby diminish side-effects, which are more frequent and severe, when the radiotherapy is given postoperatively. However, it must be recognised that selection for preoperative radiotherapy is still based on evaluation of penetration through the bowel wall, more than on possible presence of positive lymph nodes which are difficult to demonstrate because of insufficient biopsy technique and radioimmunodetection and less than optimal morphological ultrasound criteria [187].

Recent trials suggest a prolonged survival after adjuvant chemotherapy in colonic cancer Dukes' stage C [188], but the 1-year treatment is difficult to carry through, expensive and not without side-effects, making it more attractive to define that subgroup within the Dukes' C category, which will have the greatest benefit. It has previously been mentioned that some of the patients with Dukes' C cancer may have a rather good prognosis, similar to that of Dukes' B [60], but a more detailed staging will be necessary to define that subgroup. It is hoped that ongoing and future prospective trials of adjuvant chemotherapy will solve this problem, which may become even more important when combining radiotherapy and chemotherapy, which increases the risk of side effects.

Evaluation of staging procedures and treatments makes a follow-up necessary with all its possible drawbacks and advantages; it has not yet been shown that early detection of recurrent cancer will make it possible to prolong survival [189, 190], but large prospective studies are underway.

The recommendations already made by the international staging group [3], include registration of most of the prognostic factors mentioned in the present review, but changes will become necessary in the near future because of detection of new prognostic factors, especially within the field of molecular biology, diagnosis of more early cancers following screening of asymptomatic populations, and the wish to limit surgery with adjuvant therapy to patients in whom a meaningful benefit can be expected.

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Systemic Treatment of Colorectal Cancer

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INTRODUCTION

COLORECTAL CANCER (CRC) is one of the most common cancer types, second to breast cancer in women and third to lung and prostate cancer in men. The prognosis depends largely on the extent of disease at the time of diagnosis, i.e. stage according to Duke's or the TNM-system, although several other factors have been found to independently influence prognosis. To date, less than 50% of all CRC patients are cured of the disease. Despite long-standing efforts for early diagnosis in order to improve the cure rate, there is still no established screening procedure which is widely practised.

This paper deals with the systemic treatment of CRC both in metastatic disease and in the adjuvant setting. Since locoregional treatment to the liver via the hepatic artery or the portal vein is not strictly systemic treatment the reader is referred to a recent review on this specific subject by Patt *et al.* [1].

METASTATIC DISEASE

Almost by definition metastatic CRC is incurable. There are, however, a few exceptions to this. Long-term disease-free survival (or cure) can be achieved in patients undergoing surgical resection of lung or liver metastases, provided this is the only metastatic site. There are rare reports of apparent cures by chemotherapy which may be overlooked in large studies by early reporting of results [2]. However the use of chemotherapy in CRC is aimed at palliation and prolongation of survival. Endpoints for studies have been response, survival time and improvement of symptoms.

The characteristics of patients treated in a specific study is very important. Its influence on survival is higher than any treatment. Selecting patients with good prognostic factors is likely to achieve long survival even without any treatment. Prognostic factors for survival are shown in Table 1. Likewise, response to chemotherapy depends on the patients condition and other variables, though the predictability is not that good.

Table 1. Metastatic colorectal cancer: prognostic factors for survival [3, 4]

Performance status
Grade of anaplasia
Measurable disease*
Symptoms*
Elevated LDH and/or CEA and/or WBC
Lung vs. liver metastases

*Presence indicates poor prognosis.
LDH = lactate dehydrogenase; CEA = carcinoembryonic antigen; WBC = white blood cell count.

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