Multimodality Treatment of cancer of the digestive tube : the standard in 1998. Colorectal Cancer

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Introduction

Surgery is the most important part in the treatment of colorectal cancer, since only in patients where the tumour can be radically resected there is a possibility of long-term cure. Accordingly, the objectives with the surgical treatment is to achieve a loco-regional curative procedure with a good quality of life. Despite a successful operation, approximately 40-50% of all patients having had a curative resection will develop recurrent disease due to microscopic deposits not found at surgery. With different adjuvant treatment modalities the overall survival figures have increased, and today most patients have to be informed of the different treatment options available. This review will briefly discuss modern surgery and the modern view of multimodal treatment in colorectal cancer.

Surgery

An interesting observation during the last decade is the surgeon-related variable indicating that the most important factor in terms of outcome is the surgeon. This is true not only for immediate postoperative complications, but also for local recurrence rates and overall long-term results (1,2). Therefore, it is of utmost importance that surgery for colorectal cancer is done by well-trained surgeons.

Principles for radical surgery

An 'en bloc' resection of the tumour bearing bowel segment including the mesocolon/mesorectum with the regional lymph nodes is recommended. By following the anatomical cleavage during the dissection, i.e., the embryological fascias surrounding the bowel, it is possible to have a curative resection, since most tumours do respect those fascias. It has been claimed that the survival figures have improved if the 'non-touch' technique is used, but the only randomised trial exploring this question has not shown an advantage with this technique (3).

The margin along the bowel is not obvious. According to studies on distal spread in rectal cancer, a resection margin of 1-2 cm is enough (4). This finding is only adjustable in low rectal cancer, where no mesorectal lymph nodes are present. In colon cancer the proximal as well as the distal margin should not be less than 10 cm, since positive lymph nodes along the bowel in patients with a Stage III cancer, has been found as far as 7 cm from the primary lesion (5).

By following the anatomical cleavage, i.e., the embryological plane, all essential lymph nodes will be excised. The only questionable decision is how central the major vessels should be ligated. This has been studied in rectal cancer surgery, where a central ligation of the inferior mesenteric artery has been advocated among several surgeons. Although not studied in randomised trials, no data do support a central ligation, since metastatic spread to these centrally situated lymph nodes indicates generalised disease (6). Another indication that an extensive lymph node clearance might not be worthwhile is the French randomised trial on left-sided colon cancer. Patients where randomly allocated to have a sigmoid resection or a left-sided hemicolectomy, and in this study no difference in survival was demonstrated (7).

Surgery for rectal cancer

Rectal cancer surgery is known to be a difficult task, and in many countries some form of accreditation as a rectal cancer surgeon is under progress. Although not yet formalised in Sweden, it has been suggested in most guidelines in our country. To fulfil this aim special training courses have been given in all different regions, with live demonstration procedures, to learn the TME (total mesorectal excision) technique (8). Data from the literature indicate that one important prognostic factor is the circumferential margin (9), and by following the embryological plane, i.e., the rectal fascia in the posterior part of the procedure and fascia Denonvillier anteriorly, the dissection will be carried out outside the mesorectal envelope with a good chance to have cancer-free circumferential margins. Reports from different Swedish hospitals have shown that the long-term result has been improved as well as the incidence of local recurrence has decreased when this technique has been adopted more regularly (10,11).

Three main lymph node sites has to be considered during rectal cancer surgery, i.e., along the inferior mesenteric artery, laterally along the pelvic side wall, and distally to the tumour. With a 'high tie' resection the lymph nodes along the inferior mesenteric artery can easily be resected. However, by doing so the

hypogastric nerves can be damage with an increased risk of adverse effects especially in males, and most data indicates that a 'high tie' will not have an impact in long-term survival (6). A more radical approach to the lateral lymph nodes has been advocated by the Japanese surgeons, claiming that with an extended lateral lymphadenectomy, out-side the embryological mesorectal envelope, the results are improved (12). According to the Japanese data, micro metastasises have been found in the lateral lymph nodes giving the rational for a more aggressive approach. The same effect on local recurrence rates and survival can probably be achieved with adjuvant radiotherapy with much less adverse effects.

The rationale for a TME procedure is the findings of lymph node deposits in the mesorectum distally from the macroscopic tumour border (13). However, this concept with TME-surgery in all patients with rectal cancer has been criticised, mainly due to the lack of good scientific evidence but also due to the increased risk for anastomotic dehiscence and inferior bowel function as a result of a coloanal anastomosis. Based upon the knowledge of the intramural growth of the tumour rarely exceeds 0,5 cm and the introduction of the modern stapling technique most patients with mid rectal tumour could have the sphincters preserved. This is also true for many patients with a low rectal cancer and in specialised centres only 10-15% of the patients will have an abdominoperineal excision.

The drawback with TME is the subsequent consequence with a coloanal anastomosis with all known problem regarding bowel function. With a colonic J-pouch reconstruction, the bowel function will be partly restored and the functional results after a J-pouch procedure is much better than after a straight coloanal anastomosis (14). The optimum length of the limbs of the J-pouch is approximately 5-6 cm (15).

Laparoscopic resection for colorectal cancer

The rationale for using a laparoscopic approach in cancer surgery has been claimed to be a less traumatic operation and expected better cancer survival due to less immunological response (16), but no firm data has been shown in man since this hypothesis has to be tested in a prospective randomised study. The whole concept of laparoscopic surgery for colorectal cancer was more or less stopped in the 1993 due to the first reports of port-site metastases. The exact mechanism of port-site recurrence is not known, but most data indicates that bad surgical technique where the dissection in the embryological planes has not been done, is the most important factor (17).

Today laparoscopic surgery for colorectal cancer must be considered experimental treatment and should not be performed out-side randomised trials. At least six randomised trials are running today; three in Europe (UK, Spain and Northern Europe), two in the US, and one in New Zealand and Australia. Unfortunately none of these trials are large enough to answer the question, but hopefully a meta-analysis of all trials will give us a reliable answer whether or not colorectal cancer should be done laparoscopically.

Radiotherapy

Two main treatment modalities in rectal cancer exist. In patients with a mobile tumour the rationale for giving radiotherapy is to eradicate micrometastases outside the tumour bulk, which are impossible to resect at surgery. The other modality is the situation when a patient presents with a fixed tumour, i.e., 10-15% of all rectal cancers, where the rationale for radiotherapy is to achieve regression with the ultimate aim to make the tumour resectable (18).

Mobile tumour - adjuvant irradiation

Based upon tumour biology and experience from numbers of adjuvant trials, preoperative treatment is more dose effective than postoperative radiotherapy (19). The local recurrence rate after surgery can be reduced by approximately 60% if irradiation is given to a high dose level preoperatively compared with about 30-40% if the treatment is given at the same or even higher dose levels postoperatively. This substantial reduction in local recurrence rate, as has been achieved with high preoperative irradiation, does also have an impact on long term survival. Therefore, adjuvant preoperative radiotherapy should be recommended to most patients with a resectable rectal cancer. However, since the prognosis for patients with a tumour in Dukes' stage A is very good, and the risk of having a local recurrence is limited, a substantial over treatment is made if all are offered preoperative irradiation. With endorectal ultrasound imaging it is often possible to disclose this subgroup of patients in whom radiotherapy is probably superfluous.

Although all data do support that preoperative radiotherapy is a better strategy (20), several countries still use postoperative radiotherapy in the treatment of rectal cancer (21). The rationale for such a strategy is that the local stage is not known preoperatively and not until the cancer has been resected and the specimen examined by the pathologist, the real stage of disease can be determined. Another rationale is that preoperative radiotherapy with conventional fractionation's (1.8-2.0 Gy) takes 4.5-5 weeks offering a troublesome waiting delay period of almost 2 months for the patient before surgery can be performed. However, in the Scandinavian countries and in the United Kingdom a more time sparing schedule has been used for many years, with four or five daily 5 Gy fractions during one week followed by surgery the next week (22). This more cost-effective treatment is now used in several countries in Europe and has also been tested in the United States too.

If radiotherapy is combined with chemotherapy it seems that the effect might be even better regarding survival (23). However, all trials using the combined preoperative treatment have shown that toxicity will increase substantially. Thus, such a schedule may be too risky for the patients. The ideal combination of radiotherapy and chemotherapy is however not yet known, although several radiotherapy technicians and oncologists support such a combination.

Fixed tumour - treatment

This small group of patients (approximately 10-15% of all patients with rectal cancer) should be irradiated preoperatively to make the tumour resectable. In a situation with a patient presented with a fixed tumour, it is no rational to use a short-term high-dose radiotherapy since the aim with the treatment is to achieve tumour shrinkage, which is not possible with such a treatment. Therefore, the recommended treatment is with conventional fractionation to a minimum dose of 50 Gy given during a 5 weeks treatment period. After another 4 weeks of resuscitation the patient will be operated upon.

Again, chemotherapy has been used to increase the tumour killing effect of radiotherapy (24). However, toxicity is increased and no firm data do support the hypothesis that chemotherapy could have an additive effect on radiotherapy. Therefore, ongoing trials are now running comparing preoperative radiotherapy alone versus preoperative neo-adjuvant radio-chemotherapy on patients with fixed rectal cancer.

Chemotherapy

The rational of using chemotherapy is to kill micrometastases disseminated at surgery or occult metastases already present at surgery. However, the kill cell effect of modern chemotherapy is not better than the possibility of eradicating tumour masses in the size of 10^{1-3} cells indicating that chemotherapy only will in the best situation have an effect on occult micrometastases. The literature has been rather frustrating, but two main options of giving this treatment have been studies, 1) conventional intravenous treatment over a period of 6-12 months or 2) more immediate treatment with intraperitoneal or intraportal infusions one week postoperatively.

The technique used today is a biochemical modulated 5-fluorouracil (5-FU) treatment, where the 5FU effect is modulated with folinic acid or Levamisol (25). Based upon data from randomized trials there is no difference in the effect on tumour cells between those two modulation regimens of 5-FU. Today, mainly due to less toxicity 5-FU + folinic acid is the treatment of choice as an adjuvant treatment (26). New drugs are under investigations like the thymidylate synthase inhibitor Tomudex. Another drug inhibits DNA topoisomerase I (CPT 11) and new platinum complex like Oxaliplatin (27).

All data indicates that adjuvant chemotherapy should be given to all patients with tumours in Dukes' stage C. The increase in five-years survival has been estimated to approximately 10%. Although this figure looks very low, such a survival benefit is of utmost importance, since this is a common disease. A survival benefit of 10% will have an enormous impact on survival all around the world. However, there are no real scientific data supporting that patients with Dukes' stage B should have adjuvant treatment, which can be explained by the fact that rather few patients in this group do have recurrence giving it very difficult to prove if survival will improve. Theoretically there should not be any difference but the effect is more difficult to demonstrate (28).

Postoperative inravenous 5-FU

This treatment should start as early as possible and in most protocols a twelve months treatment has been recommended. Ongoing trials are testing if six months could be enough. In some protocols is the treatment given during one week and repeated every third week for a year. Other treatment options are two days every second week for twelve months.

Intraportal 5-FU

In 1985 a survival benefit was reported from a British trial if patients with colorectal cancer were treated with intraportal 5-FU infusions for one week postoperatively (29). Since that trial was published several studies have been done to explore whether or not this one-week treatment could have an impact on survival. A meta-analysis performed on all randomized trials (more than 6,000 patients included) does indicate that there is a slight survival benefit with intraportal 5-FU treatment as an adjuvant setting for patients with colorectal cancer. The survival benefit has been estimated to be in the range of 5-10%. This is of the same magnitude as have been reported from the metaanalysis regarding postoperative intravenous treatment. Therefore, a relevant discussion is whether one week treatment given intraportally during the first postoperative week while the patients are staying at the hospital or for six months up to one year as a postoperative infusion therapy should be recommended. Regarding costs it is obvious that the short term treatment is the better, but the cancer effect is not unequivocally better since no randomized trial has compared those two regimen.

Intraperitoneal treatment

The third option with adjuvant treatment is to use intraperitoneal chemotherapy. The rational with this type of treatment is to take advantage of the local effect by chemotherapy on the resection area in the abdomen.

It has been shown that 5-FU is quickly absorbed and more or less 100% of the 5FU administered intraperitoneally goes to the liver via the portal vein. Therefore it is presumed that this administration form is likely to have the same effect on occult metastases in the liver as after intraportal infusion as well as with intravenous treatment. The advantage with both intraportal and intraperitoneal infusion seems to be that toxicity is more less compared with intravenous treatment. Some randomized trials have been done with this treatment options, but it is still too early to know whether this is as good as intraportal treatment or even as good or better than intravenous treatment (30).

Immunotherapy

A third option to improve long-term survival with an adjuvant setting is immunotherapy. The antitumour mechanism with such a modality is indirectly via modulation of the host's response to the tumour and theoretically immunotherapy could be less toxic and data supports that the use of monoclonal antibodies in patients with micrometastases could be better regarding both effect and toxicity than adjuvant chemotherapy. One advantage with monoclonal antibodies is the acting mechanism by binding to the antigens on the tumour cells which dose occur in both dividing cells and dormant cells. Chemotherapy and radiotherapy can only have an effect on dividing cells, which limitates their effect on the majority of all tumour cells.

It is not to be expected that monoclonal antibodies could have an effect on too large tumour burdens like macroscopic metastases. The effect is theoretically best on small occult micrometastases giving a prefect drug for adjuvant setting, i.e., no toxicity and good killing effect even in dormant cells. This has also been the case in one randomised trial where patients whom received the monoclonal antibody 17-1A postoperatively were compared with those having surgery alone (31). The survival benefit found in the only trial reported so far was of the same magnitude as for adjuvant chemotherapy. Ongoing trials in both the United States and Europe are comparing conventional chemotherapy (5-FU + folinic acid) versus monoclonal antibodies (17-1A).

References

1. MC ARDLE C.S., HOLE D. Impact of variability among surgeons on postoperative morbidity and ultimate survival. *Br. Med. J.*, 1991, **302** : 1501-1505.
2. HERMANEK P., WIEBELT H., STIMMER D., RIEDL S. Prognostic factor of rectum carcinoma — Experience of the German multicentre study SGCRC. *Tumori*, 1995, **81** (suppl) : 60-64.
3. WIGGERS T., JEEKEL J., ARENDS J.W., BRINCKHORST, KLUCK H.M., LUYK C.I. *et al.* Non-tough isolation technique in colon cancer : A controlled prospective trial. *Br. J. Surg.*, 1988, **75** : 409-415.
4. WILLIAMS N.S., DIXON M.F., JOHNSTON D. Reappraisal of the 5 centimetre rule of distant excision for carcinoma of the rectum : A study of distal intramural spread and of patients' survival. *Br. J. Surg.*, 1983, **70** : 150-154.
5. TOYOTA S., OHTA H., ANAZAWA S. Rationale for extent of lymph node dissection for right colon cancer. *Dis. Colon Rectum*, 1995, **38** : 705-711.
6. PEZIM M.E, NICHOLLS R.J. Survival after high or low ligation of the inferior mesenteric artery during curative surgery for rectal cancer. *Ann. Surg.*, 1984, **200** : 729-733.
7. ROUFFET F., HAY J.M., VACHER B., FINGERHUT A., EL-HADAD A., FLARNANT Y. *et al.* Curative resection for left colonic carcinoma : Hemicolectomy vs. segmental colectomy : A prospective, controlled, multicentertrial. *Dis. Colon Rectum*, 1995, **37** : 651-659.
8. HEALD R. J. Total mesorectal excision is optimal surgery for rectal cancer : a Scandinavian consensus. *Br. J. Surg.*, 1995, **82** : 1297-1299.
9. ADAM L.T., MOHAMDEE M.O., MARTIN E.G., SCOTT N., FINAN P.J., JOHNSTON *et al.* Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet*, 1994, **344** : 707-711.
10. ARBMAN G., NILSSON E., HALLBÖÖK O., SJÖDAHL R. Local recurrence following total mesorectal excision for rectal cancer. *Br. J. Surg.*, 1996, **83** : 375-379.
11. DAHLBERG M., PÅHLMAN L., BERGSTRÖM R., GLIMELIUS B. Improved survival in patients with rectal cancer : a population based register study. *Br. J. Surg.*, 1998, **85** : 515-520.
12. KOYAMA Y., MORIYA Y., HOJO K. Effects of extended systematic lymphadenectomy for adenocarcinoma of the rectum - significant improvement of survival rate and decrease of local recurrence. *Jpn. J. Clin. Oncol.*, 1984, **14** : 623-632.
13. SCOTT N., JACKSON P., AL-JABERI T., DIXON M.F., QUIRKE P., FINAN P.J. Total mesorectal excision and local recurrence : a study of tumour spread in the mesorectum distal to rectal cancer. *Br. J. Surg.*, 1995, **82** : 1031-1033.
14. HALLBÖÖK O., PÅHLMAN L., KROG M., WEXNER S.D., SJÖDAHL R. Randomized comparison of straight and colonic J-pouch anastomosis after low anterior resection. *Ann. Surg.*, 1996, **224** : 58-65.
15. HIDA J., YASUTOMI M., FUJINOTO K., OKUNO K., IEDA S., MACHIDERA N. *et al.* Functional outcome after low anterior resection with low anastomosis for rectal cancer using the colonic J-pouch. Prospective randomized study for determination of optimum pouch size. Dis Colon Rectum, 1996, **39** : 986-991.
16. BOUVY N.D., MARQUET R.L., JEEKEL J., BONJER H.J. Laparoscopic bowel resection in the rat : improved postoperative recovery and less tumour take. *Surg. Endosc.*, 1996, **10** : 490-494.
17. PÅHLMAN L. The problem of port-site metastases after laparoscopic cancer surgery. *Ann. Med.*, 1997, **29** : 477-481.
18. PÅHLMAN L., GLIMELIUS B. Radiotherapy. *In* : NICHOLLS R.J., DOZOIS R.R. (eds). Surgery of the Colon & Rectum, London : Churchill Livingstone, 1997, 475-491.
19. GLIMELIUS B., ISACSSON U., JUNG B., PÅHLMAN L. Radiotherapy in addition to radical surgery for rectal cancer — evidence for a dose-response effect favouring preoperative treatment. *Int. J. Radiat. Oncol. Biol. Phys.*, 1997, **37** : 281-287.
20. PÅHLMAN L., GLIMELIUS B. Pre- and postoperative radiotherapy in rectal carcinoma : report from a randomized multicenter trial. *Ann. Surg.*, 1990, **211** : 187-195.
21. KROOK J.E., MOERTEL C.G., GUNDERSON L.L. *et al.* Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N. Engl. J. Med.*, 1991, **324** : 709-715.
22. SRCT (Swedish Rectal Cancer Trial) : Improved survival with preoperative radiotherapy resectable rectal carcinoma. *N. Engl. J. Med.*, 1997, **336** : 980-987.
23. VON DER MAASE H. Experimental studies on interactions of radiation and cancer chemotherapeutic drugs in normal tissues and a solid tumour. *Radiother. Oncol.*, 1986, **7** : 47-68.
24. FRYKHOLM G, PÅHLMAN L, GLIMELIUS B. Preoperative irradiation with and without chemotherapy (MFL) in the treatment of primarily nonresectable adenocarcinoma of the rectum. Results from two consecutive studies. *Eur. J. Cancer Clin. Oncol.*, 1989, **25** : 1535-1541.
25. MOERTEL C.G., FLEMING T.H., MACDONALD J.S. *et al.* Fluorouracil plus levamisole after resection of stage m colon carcinoma : a final report. *Ann. Intern. Med.*, 1995, **122** : 321-326.
26. HALLER D.G., CATALANO P.J., MACDONALD J.S. *et al.* Fluorouracil, leucovorin and levamisole adjuvant therapy for colon cancer ; four-year results of INT-0089. *Proc. Am. Soc. Clin. Oncol.*, 1997, **16** : 265a.
27. CONROY T. Single-agent chemotherapy of colorectal cancer. *In* : BLEIBERG H., ROUGIER P., WILKE H.J. (eds). Management of colorectal cancer. London : Martin Dunitz, 1998, 211-220.
28. MAMOUNAS E.P., ROCKETTE H., JONES J. *et al.* Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B vs dukes' C colon cancer : results from four NSABP adjuvant studies. *Proc. Am. Soc. Clin. Oncol.*, 1996, **15** : 205.

29. TAYLOR I., MACHIN D., MULLEE M. *et al.* A randomised controlled trial of adjuvant portal vein cytotoxic liver perfusion of colorectal cancer. *Br. J. Surg.*, 1985, **72** : 359-363.
30. GRAF W., WESTIN J.-E., PÅHLMAN L., GLIMELIUS B. Adjuvant intraperitoneal 5-fluorouracil and intravenous leucovorin after colorectal cancer surgery : a randomized phase II placebo-controlled-study. *Int. J. Colorect. Dis.*, 1994, **9** : 35-39.
31. RIETHMÜLLER G., SCHNEIDER-GADICKE E., SCHLIMOK G. Randomised trial of monoclonal antibody for adjuvant treatment of resected Dukes C colorectal carcinoma. *Lancet*, 1994, **343** : 1177-1183.