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Follow Up and Recurrence of Colorectal Cancer

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1. Introduction

Despite optimal primary treatment, with adequate surgery with or without adjuvant chemotherapy, ~30%–50% of patients with colon cancer will relapse and die of their disease. The principal aim of follow-up programmes after curative resection of colorectal cancer is to improve survival (Gan et al., 2007). To achieve this goal, patients are screened for early recurrent disease with the intent of a second curative surgery. Patients with a history of colorectal cancer are also at risk to develop new primary colorectal cancers (CRC). The risk of development of new primary lesions has been estimated to 0,35% per year (Cali et al., 1993). Bouvier et al reported the incidence of metachronous cancer as being 1.8% at five years, 3.4% at 10 years, and 7.2% at 20 years with the greatest excess risk between one and five years post-surgery(Bouvier et al. 2008).
The main sites of colorectal cancer relapse are listed in table 1 (Figueredo et al., 1993).

Colorectal cancer relapse	Colon cancer	Rectum
	%	%
Liver	35	30
Lung	20	30
Peritoneum	20	20
Retroperitoneum	15	5
Peripheral lymphonodes	2	7
Local relapse	15	35
Other (brain, bones)	<5	<5

Table 1. Sites of colorectal cancer relapse

To evaluate the stage of the disease, treatment strategy and prognosis a combination of investigations is necessary. In the past there was no strong evidence that regular follow-up could improve the outcome for patients radically resected for colon cancer. As follow-up can be expensive and resource consuming in terms of both money and procedures, an intensive

surveillance needs to be justified with a good level of evidence. The more effective the treatment of patients with colorectal cancer, the less cost-effective is the follow-up with regard to diagnosis of a relapse.

Although most patients with relapsed colorectal cancer are inoperable at the time of diagnosis, one third of patients with isolated locoregional or distant metastases survive 5 years (Browne et al., 2005). Number of resected patients for relapse is increasing - about 20% of patients with liver metastases are indicated for surgery (Guyot et al., 2005). Other patients are operated after downstaging after chemotherapy or chemoradiotherapy. Long-term survival is also achieved after resection of pulmonary metastases, even when combined of liver and lung metastases resection (Ike et al., 2002). It is evident that high-risk patients (TNM II, III) with relapse diagnosed using imaging and endoscopic techniques have better survival than patients who had clinically evident relapse (Chau et al., 2004). Even patients, who are at the time of relapse diagnosis inoperable, had improved survival due to new palliative chemotherapy regimes (Ahmed et al., 2004).

Due to the different localization of possible recurrence, we cannot use one diagnostic tool, we need a combination of various imaging and laboratory methods. In the first two to three years after resection of primary tumor incidence of relapse increases exponentially, then passes into the plateau (Griffin et al., 1987; Scholefield et al., 2002). Therefore, diagnostic schedule must be adapted. Finally, the postoperative monitoring of patients after curative resection has psychological effects. It can be both positive and negative. Positive involves calming the patient and aid in further treatment. Negative effects includes a sense of false security when relapse is undetected.

Any follow-up system combines a number of tests, whether clinical, laboratory and imaging, as well as their frequency.

Meta-analyzes of studies concludes that intensive follow-up shows a statistically significant difference in overall 5-year survival rate of patients after curative surgery for colorectal cancer, and can diagnose relapse in curable stage, especially if located in the liver and lungs (Tjandra & Chan, 2007; Rosen et al., 1998). In the case of relapse in rectal cancer, studies indicate the minor importance of intensive follow-up (Secco et al., 2000). Analysis showed no significant difference in the incidence of relapse among patients in groups with minimal versus intensive monitoring system, however, closely monitored group had significantly higher number of surgical interventions for recurrence, which is given by an earlier diagnosis and thus a higher resectability of recurrence.

Studies previously conducted and their meta-analyses may be problematic because of non-standard combinations of investigations and also non-standard frequency. Intensive follow-up study in one study is very similar to that in other studies considered to be less intense (Jeffery et al., 2007).

2. Recomendations for follow-up

Diagnostic tools used for follow-up can be dividend in to:

- Imaging procedures
- Endoscopic techniques
- Laboratory tests
- History and physical examination

2.1 Recommendations arising from the meta-analyzes

- for patients at high risk of relapse (stages IIb and III)
  - clinical examination, carcinoembrionic antigen (CEA), chest radiograph, ultrasonography of liver or computer tomography scan (CT) every 6 months for first postoperative 3 years, 3 next years with a frequency of one year
- if the recurrence is detected the patient should be discussed in the multidisciplinary oncology team (surgeon, radiologist, oncologist) to consider the best course of treatment
- for patients at high risk of relapse with comorbidities or other barriers
- clinical examination every year
- for all patients with resected colorectal cancer
- colonoscopy with the polypectomy 1 x per year, in the absence of polyps every 3-5 years(Tjandra & Chan, 2007; Rosen et al., 1998).

2.2 American Society of Clinical Oncology (ASCO) recommendations

Imaging Procedures:

Computed tomography (CT). Patients who are at higher risk of recurrence, and who could be candidates for curative-intent surgery, should undergo annual computed tomography of the chest and abdomen for 3 years after primary therapy for colon and rectal cancer. A pelvic CT scan should be considered for surveillance after rectal cancer therapy, especially for patients who have not been treated with radiotherapy.
Chest x-ray. Annual chest x-rays are *not* recommended.

Endoscopic Techniques:

Colonoscopy. All patients with colon and rectal cancer should have a colonoscopy for the pre- or perioperative documentation of a cancer- and polyp-free colon. After the surgical treatment of colorectal cancer, ASCO recommends the surveillance guideline presented by the American Gastroenterological Association (AGA): a colonoscopy at 3 years and, if normal, every 5 years thereafter (Winter et al, 2003).
Flexible proctosigmoidoscopy (rectal cancer). For patients who have not received pelvic radiation, flexible sigmoidoscopy of the rectum every 6 months for 5 years is recommended.

Laboratory Tests

Tumor markers (Rocker et al., 2006): For colorectal cancer, it is recommended that carcinoembryonic antigen (CEA) be ordered preoperatively, if it would assist in staging and surgical planning. Postoperative CEA levels should be performed every 3 months for stage II and III disease for at least 3 years if the patient is a potential candidate for surgery or chemotherapy of metastatic disease. CEA is the marker of choice for monitoring the response of metastatic disease to systemic therapy. Data are insufficient to recommend the routine use of p53, ras, thymidine synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase, microsatellite instability, 18q loss of heterozygosity, or deleted in colon cancer (DCC) protein in the management of patients with colorectal cancer. For pancreatic cancer, carbohydrate antigen 19-9 (CA 19-9) can be measured every 1 to 3 months for patients with locally advanced or metastatic disease receiving active therapy. Elevations in serial CA 19-9 determinations suggest progressive disease but confirmation with other

studies should be sought. *Blood tests.* Routine blood tests (i.e., CBCs or liver fiction tests) are not recommended.
Fecal occult blood test. Periodic fecal occult blood testing is not recommended.
Laboratory-derived prognostic and predictive factors. Until prospective data are available, use of molecular or cellular markers should not influence the surveillance strategy (Desch et al., 2005).

2.3 European Group On Tumour Markers (EGTM) recommendations

For identifying recurrences in patients with previously diagnosed colorectal cancer, CEA has a sensitivity of about 80% (range 17-89%) and a specificity of approximately 70% (range 34-91%). Early studies showed that serial CEA levels could detect recurrent disease many months (usually 4-10 months) in advance of clinical evidence of disease (Fletscher, 1986). CEA testing was found to be most sensitive for diagnosing hepatic or retroperitoneal disease and relatively insensitive for either local, peritoneal or pulmonary involvement (Moertel et al., 1993). Some investigators have reported that a slowly rising CEA usually indicates a locoregional recurrence while rapidly increasing levels usually suggest hepatic metastasis (Begent, 1984).
In the follow-up of patients with colorectal cancer, the optimum interval between CEA measurements has not been established. In practice, most clinicians use intervals of 3 months, at least for the first 2 years after the initial diagnosis.
Clearly, further work is necessary to address the impact of CEA monitoring on patient survival, quality of life and cost of care. Ideally, this study should be carried out as part of a prospective randomised trial.
Although surgery remains the most effective therapy for colorectal cancer, chemotherapy is finding increasing use especially in patients with advanced disease. Administration of this therapy may however, cause transient elevations in CEA levels.
While CEA is the preferential biochemical test for colorectal cancer, a number of other markers such as CA19-9, CA242 and cytokeratins (e.g., TPA and TPS) have also been evaluated for this malignancy. While some of these markers have been found to complement CEA, further work will be required to see which marker is most complementary to CEA.

2.4 European Society for Medical Oncology (ESMO) recommendations

- Intensive follow-up must be performed in colon cancer patients [I, A].
- History and physical examination and CEA determination are advised every 3–6 months for 3 years and every 6–12 months at years 4 and 5 after surgery [II, B].
- Colonoscopy must be performed at year 1 and thereafter every 3–5 years looking for metachronous adenomas and cancers [III, B].
- CT scan of chest and abdomen every 6–12 months for the first 3 years can be considered in patients who are at higher risk for recurrence [II, B].
- Contrast enhanced ultrasound imaging (CEUS) could substitute for abdominal CT scan [III, C].
- Other laboratory and radiological examinations are of unproven benefit and must be restricted to patients with suspicious symptoms.(Labianca et al., 2010)

2.5 National Comprehensive Cancer Network (NCCN) guidelines

- History and physical examination every 3-6 months for 2 years, then every 6 months for a total of 5 years
- CEA every 3-6 months for 2 years , then every 6 months for a total of 5 years
- CT scan of abdomen and pelvis annually for 3 years
- Colonoscopy at 1 year , then as clinically indicated(NCCN, 2011)

2.6 Guidelines British Columbia Medical Associattion (BCMA)

Recommendation 1: Clearing colonoscopy

Ideally, colonoscopy should be performed pre-operatively. If this is not feasible, then it may be done three to six months post-operatively if no metastases were found. Air-contrast barium enema combined with sigmoidoscopy is an acceptable alternative where colonoscopy is not readily available.

Recommendation 2: Post-operative follow-up

After recovery from surgery, visits should only be scheduled as needed. The routine use of liver enzyme tests and abdominal ultrasound is not recommended in the absence of symptoms.

Recommendation 3: Tumour markers

The value of carcinoembryonic antigen (CEA) testing in the post-operative period is controversial and its usefulness is therefore limited. However, in individuals who would be candidates for resection of isolated hepatic or pulmonary metastases, serial measurement of CEA levels post-operatively (every three months for two years) may be of value in detecting recurrence that is treatable in up to 25 per cent of patients.

Recommendation 4: Prevention of new cancers

Repeat colonoscopy once every three years until no new adenomas are discovered. Thereafter, repeat colonoscopy every five years until the detection of new tumours is unlikely to influence the patient's lifespan. Air-contrast barium enema combined with sigmoidoscopy is an acceptable alternative where colonoscopy is not readily available.

Recommendation 5: Low rectal cancer

For patients who have undergone low anterior resection of rectal cancers, digital rectal examinations and proctoscopy or sigmoidoscopy should be undertaken at three months, six months, one year and two years to look for anastomotic recurrence. Thereafter, recommendation 4 should be followed.(BCMA, 2011)

2.7 Australian Clinical Practice Guidelines (CCA)

The Australian *Clinical Practice Guidelines for the prevention, early detection and management of CRC, 2nd edition, 2005* proposed that follow-up should be offered to all patients who have undergone curative surgery and are fit for further intervention if disease is detected. This includes patients who have had malignant polypectomy or curative endoscopic resection of Stage I CRC but excludes patients with Stage IV CRC if their treatment does not offer the possibility of cure.

Patients with proved Lynch syndrome (HNPCC or hereditary non-polyposis colorectal cancer), should continue to have annual surveillance colonoscopy performed post-

operatively because of the apparent rapid progression of neoplasia from adenoma to carcinoma.

Patients including those whose initial diagnosis was made younger than 40 years of age, with probable or possible HNPCC (i.e. patients whose tumours are MSI-high and less than 50 years old at time of initial cancer diagnosis but not proved by genetic testing to have HNPCC), with hyperplastic polyposis and BRAF mutation and with multiple synchronous cancers or advanced adenomas at initial diagnosis should be considered following surgery to continuing with more frequent surveillance than would otherwise be recommended (e.g. initial post-operative colonoscopy at one year and then annually, second-yearly or third-yearly. (CCA, 2011)

Summary in reccomendations for follow-up see in table 2.

	Metaanalyses	ASCO	EGTM	ESMO	NCCN	BCMA
CEA	every 6 months	every 3 months	every 3 months	every 3-6 months	every 3-6 months for 2 years , then every 6 months	every 3 months for two years
Colonoscopy	every 6 months	3 years after surgery		In 1 year, and thereafter every 3–5 years	at 1 year , then as clinically indicated	3-6 months after surgery
History, physical examination	every 6 months			every 3-6 months	every 3-6 months for 2 years, then every 6 months	as needed
Chest X ray		not reccomended				
CT	every 6 months	3 years after surgery		every 6–12 months for the first 3 years	annually for 3 years	
Ultrasound	every 6 months			CEUS could substitute for abdominal CT scan		

Table 2. Summary of follow up recommendations

3. Discussion

The optimal combination and frequency of investigations in follow-up of patients after CRC resection has not been determined. Importantly, the performance of annual colonoscopy has not been shown to improve five-year survival.

Studies comparing intensive and less intensive follow up programes were conducted in many countries around the World. In Finland(Makela et al., 1995) randomized more than 100 patients. Less intensive follow up system included either rigid sigmoideoscopy (for rectal or sigmoid cancer) or barium enema (for colon cancer) once a year. Patients in intensive arm underwent colonoscopy within 3 months of surgery and then yearly colonoscopy thereafter, liver ultrasound every 6 months and CT scans every year. Intensive follow up programe significantly earlier identified recurrence, there were no signifiant diference in resecability rates and five-year survival. Ohlsson et al. showed the same results on 107 patients (Ohlson et al., 1995). In Italy, (Pietra et al., 1998) randomized more than 200 consecutive patiens into low intensity follow up arm (physical examination, liver ultrasound and CEA at 6 month and then yearly, colonoscopy and chest X ray annually) and intensive arm (clinical controls, liver ultrasound, CEA each 3 months during the first 2 years, at 6 month interval for the next 3 years and then yearly, colonoscopy, chest X ray and CT scan yearly). Intensive group demonstrate statistically signifiant increase in five-year survival (73,1% vers. 58,3%). Kjeldsen and coleagues randomized big group up to 600 patients to frequent and minimal follow up arms and demonstrated significantly earlier detection of recurrence, but not improvement of overall or cancer-related five-year survival (Kjeldsen et al., 1997).

Then, metaanalyses were conducted. Renehan and colleagues involved 1342 patients and demonstrated a signifiant improvement in overall five-year survival in intensivelly followed patiens. The intensive follow-up groups were also associated with significantly earlier detection of all recurrences and isolated local recurrences (Renehan et al., 2002). A meta-analysis by Tjandra et al concluded that intensive follow-up increased the re-resection rate for recurrent disease and improved overall survival but the survival advantage was not due to earlier detection of recurrence and cancer-related mortality was no better (Tjandra & Chan, 2007). Forty-one centers have participated in the GILDAtrial. There are 39 centers in Italy, one in Spain, and one in the United States. Both the less intensive follow-up group and the more intensive follow-up group are well matched for distribution of sex, age, cancer stage (Dukes B or C) and primary site of cancer (colon or rectum). This trial will allow us to quantify the lead-time provided by the specifically defined intensive follow-up regimen, and to compare the likelihood of uncovering recurrent disease amenable to salvage therapy (Grossmann et al., 2004).

3.1 Imaging procedures – New possibilities

3.1.1 Computed Tomographic Colonography (CTC)

CTC has been introduced in the last decade for the identification of colorectal lesions, polyps and cancer (Reuterskiold et al., 2006). CTC is being increasingly used for the radiological evaluation of colorectal symptoms. There have been a few publications on the use of CTC in follow-up of these patients after surgery (Amitai et al., 2009). CTC has the advantage in demonstrating the inner surface of the colon tube simulating the endoscopic colonoscopic

view and demonstrating the pericolonic structures at the same time. It has a high accuracy in detecting colonic neoplasia (Halligan et al., 2005).

3.1.2 PET/CT scan

In past 10 years PET/CT scan was introduced as a standard method for colorectal cancer imaging, especially for distant metastases diagnosis. Studies comparing PET/CT scan with standard methods showed superiory of this paging method. In these studies (Deleau et al., 2011; Han et al., 2011) data of patients with suspected CRC recurrence and in whom both FDG-PET/CT and CT were performed were analyzed. All detected lesions were characterized according to their number, size, and localization. In Deleau´s study 171 true-positive lesions were identified in 71 patients. CT scan was positive in 58 (82%) patients and FDG-PET/CT in 70 (98%) patients. In per lesion analysis, the global accuracy of FDG-PET/CT in detection of lesions was of 88% (sensitivity = 95%, specificity = 54%), which was higher than that of CT (53%, sensitivity = 55%, specificity = 43%), particularly in case of lymph nodes metastases (100 vs. 35%) and locoregional lesions (100 vs. 39%). FDG-PET/CT modified the clinical management in 31 patients.

At present, whole-body (18)F-FDG PET/CT is an advanced diagnostic imaging technique in detecting loco-regional recurrence and metastasis in postoperative patients with colorectal carcinoma for its higher sensitivity and specificity and also appears to be useful modality in evaluating chemotherapy response and can differentiate responders from nonresponders in recurrent CRC patients (Shamim et al., 2011).

3.1.3 Contrast enhancement ultrasound scan

There were few studies done to compare the sensitivity and specificity of contrast-enhanced ultrasonography (CEUS) and computed tomography (CT) in the detection of liver metastases in patients with colorectal cancer (Larsen et al., 2009). In this Denmark study 365 patients were included. All patients had undergone preoperative US, CEUS and Multidetector CT and 65.5% had received Intraoperative US. Multidetector CT found significantly more metastases than CEUS. In a patient-by-patient analysis MDCT had a non-significantly higher sensitivity in the detection of liver metastases compared to CEUS . The specificity of was slightly better than that of MDCT. Multidetector CT found significant more metastases than CEUS. In previous study, held by same authors (Larsen et al., 2007), sensitivity and specificity of contrast enhanced ultrasonography (CEUS) with conventional ultrasonography (US) in detection of liver metastases in patients with colorectal adenocarcinoma were compared. In 461 patients contrast enhanced ultrasonography improved the sensitivity significantly in detection of liver metastases from 0.69 by US to 0.80 ($p=0.031$). In 24 patients, CEUS found a higher number of metastases than US ($p<0.001$). The specificity (0.98) and the positive predictive value (0.86) was the same.

In Italian study (Piscaglia et al., 2007) a total of 109 patients with colorectal (n = 92) or gastric cancer prospectively underwent computed tomography (CT) scan and conventional US evaluation followed by real time CEUS. A diagnosis of metastases was made by CT or, for lesions not visible at CT, the diagnosis was achieved by histopathology or by a malignant behavior during follow-up.

Of 109 patients, 65 were found to have metastases at presentation. CEUS improved sensitivity in metastatic livers from 76.9% of patients (US) to 95.4% , while CT scan reached

90.8%. CEUS and CT were more sensitive than US also for detection of single lesions In 15 patients (13.8%), CEUS revealed more metastases than CT, while CT revealed more metastases than CEUS in 9 patients (8.2%) Piscaglia concluded that CEUS is more sensitive than conventional US in the detection of liver metastases and could be usefully employed in the staging of patients with gastrointestinal cancer. Findings at CEUS and CT appear to be complementary in achieving maximum sensitivity.

3.2 Endoscopic techniques

Colonoscopy: Surveillance colonoscopy after CRC resection has the theoretical potential to improve patient outcome by finding metachronous cancers at an early stage, detecting luminal/ anastomotic cancer recurrences and removing metachronous adenomas. Nevertheless, studies have differed in their conclusions about the overall effectiveness of colonoscopic surveillance. Recommendations about the timing of colonoscopy after CRC resection should be based upon the "natural history" of metachronous colonic neoplasia, in order to meet the objectives of surveillance, namely early detection of metachronous cancer and timely polypectomy for metachronous adenomas.

Patients undergoing either local excision (including transanal endoscopic microsurgery) of rectal cancer or advanced adenomas or ultra-low anterior resection for rectal cancer should be considered for periodic examination of the rectum at six monthly intervals for two or three years using either digital rectal examination, rigid proctoscopy, flexible proctoscopy, and/or rectal endoscopic ultrasound. These examinations are considered to be independent of the colonoscopic examination schedule (CCA, 2011).

Two recent case-control studies of colonoscopy suggest that colonoscopy is not as effective in decreasing mortality (Baxter et al., 2009) or incidence of right-sided cancer (Lakoff et al., 2008). A recent investigation of surveillance colonoscopy found that subjects were more likely to develop recurrent adenomas in the same colon segment, suggesting that particular attention be paid to where a previous adenoma has been removed (Pinsky et al., 2009).

Leung and colleagues studied colorectal cancer risk despite surveilance colonoscopy and concluded that despite frequent colonoscopy there was a persistent ongoing risk of cancer in the years after the trial. Subjects with a history of advanced adenoma are at increased risk of subsequent cancer and should be followed closely with continued surveillance (Leung et al., 2010).

Importantly, the performance of annual colonoscopy has not been shown to improve five-year survival.

3.3 Laboratory tests

Based on literature and also our results (Lipská et al., 2007), it can be concluded that monitoring of the tumor markers is valuable, mainly in those cases where preoperative CEA and/or CA19-9 were elevated. The level of CEA and CA19-9 increases according to the pTNM stage of the disease. CEA or CA19-9 below the cut-off level does not exclude even a very advanced colorectal cancer. To evaluate the stage of the disease, treatment strategy and prognosis a combination of investigations is necessary. Surveillance based only on CEA and/or CA19-9 is cost-effective, but does not disclose more than 1/3 of patients with relapse. In general practice CEA is often used as the only parameter in the follow-up

regimens. Based on this system, CEA seems highly effective, but when other investigations are included, 1/3 of relapsed patients are diagnosed by a method other than CEA.
Non-invasive screening of molecular biomarkers(such as cell-free tumor DNA) may enable effective surgical intervention through an early diagnosis of the disease. To determine the most appropriate diagnostic and therapeutic strategy we need to know not only clinical and histological factors but also molecular factors of the tumor. New impromvent in molecular biology should open the way to new perspectives in research of carcinogenesis, medical (targeted therapy) and surgical treatment (in the appropriate moment and appropriate extent). There has been increased interest in identifying biologic indicators that may help better define patients at risk for recurrence.

3.4 Author´s experience

At Surgical Department of Thomayer University Hospital, Charles University Prague, there is for more than 15 years intensive system of follow-up applied. See table 3.

	Months after operation														
	3	6	12	18	24	30	36	42	48	54	60	72	84	96, 120	108, 144, 166
History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CEA, CA19-9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ultrasonography	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT			X		X		X		X		X	X	X	X	X
Coloscopy			X		X		X		X		X	X	X	X	X
Chest X ray					X				X			X		X	
PET, PET/CT	In the case of unsolved elevation in markers or before reoperation														

Table 3. Follow-up system in Thomayer University Hospital

Four follow-up studies (based on different tumor markers, CT scan, PET/CT scan, ultrasonography and other investigations) performed on author´s department are reported.

3.4.1 Study 1

Aim: To evaluate CEA and CA19-9 in a long-term follow-up after radical surgery for colorectal cancer.
Patients and Methods: A total of 1090 patients were operated on for colorectal cancer, 716 patients underwent R0 resection, 631 patients were under further surveillance, relapse was diagnosed in 122 patients (20%), 74 patients were indicated for reoperation The resectability of the relapse was 35%. An AxSYM instrument (Abbott) was used for analysis.

Results: At the time of relapse both markers were normal in 31% of the patients. When relapse was diagnosed, in patients with normal preoperative levels, CEA and CA19-9 were below cut-off in 48% and 79% of cases respectively, and in those with primary elevation, they were again elevated in 78% and 64% of cases respectively.
Conclusion: The surveillance based only on CEA and /or CA19-9 was cost-effective, but failed to disclose 1/3 of patients suffering from relapse; markers must be combined with liver and chest imaging methods and colonoscopy.

3.4.2 Study 2

The aim of the study was to investigate the clinical significance of serum tumor markers and biological activity markers - oncofetal tumormarker CEA, mucin tumormarkers CA19-9, CA242, proliferative tumor markers Thymidine kinase, soluble cytoceratines fragments TPS, TPA, adhesive molecules ICAM - 1, VCAM -1, IGF-1, and adipocytokinins Adiponectin, Leptin in patients with colorectal cancer before primary operation. The study included 142 patients between the ages of 35 - 89 years. We confirmed that CA19-9 is besides CEA an important marker in colorectal cancer. Comparing CA19-9 and CA242 in preoperative staging, CA242 is more specific. Statistical significant difference between early and metastatic stage of colorectal cancer was not confirmed in markers: ICAM-1, VCAM, adiponectin, leptin. Statistical significant difference between early and metastatic stage of colorectal cancer was confirmed in markers: CEA, CA19-9, CA242, TPS, TPA, TK, IGF-1. None of the used markers was able to distinguish stage II and III, in other words to identify patients with infiltration of lymph nodes. This fact is very important in our aspirations to find which marker from periferal blood could help to identify patiens at risk of lymphatic infiltration and select these patients for adjuvant therapy. Combination of CEA and either CA19-9 or CA242 can be recommended for preoperative investigation. CA 242 in this study seems to have slightly better results in preoperative staging (Levý et al., 2008).

3.4.3 Study 3

Aims: To investigate presence of cell-free tumor DNA and its correlation to clinical status of the patient, especially metastatic liver disease. There has been increased interest in identifying biologic indicators that may help better define patients at risk for recurrence after hepatic resection for colorectal metastases.
Methods: In a prospective study cohort of 108 patients we have initially acquired a tissue samples from primary tumor (n=108). Where available, additional tissue was collected from nodes and liver metastases. For each patient, multiple plasma samples were acquired over a period covering initial examination, immediately preceding the surgery, at the surgery, post-surgery and during a subsequent follow-up. We have used the most frequent colorectal somatic mutations (APC, TP53, BRAF, PIK3CA and KRAS) detected in primary tumors to trace cell-free tumor DNA in plasma samples.
Results: A total of 66 patients (66/108, 415%) had somatic mutation in primary tumor. From these 66 patients in 57 patients the plasma samples were examined. Where available, mutation from primary tumor was also confirmed in the metastatic liver tissue (4/4, 100%). Cell-free tumor DNA was detected in plasma according to TNM stages in 0%, 10%, 28% and 100% respectively. In 2 patients positivity was detected in subsequent plasma samples, following the course of the disease development.

Conclusion: Our results indicate a potential for the detection of cell-free tumor DNA as a non-invasive test of metastatic liver disease. Somatic mutations in additional genes (BRAF, PIK3CA) are now being explored as markers to increase the number of patients that can be evaluated from cell-free tumor DNA.

3.4.4 Study 4

Aim of the study:The conventional diagnostic techniques used to assess recurrence of colorectal cancer (CRC) often yield unspecific findings. Integrated FDG-PET/CT seems to offer promise for the differential diagnosis of benign and malignant lesions. The aim of this study was to compare the value of FDG-PET and PET/CT in the detection of CRCR subsequent to colonic resection or rectal amputation.
Methods:The population for this retrospective study comprised 84 patients with suspected CRC. The sensitivity, specificity and accuracy of PET and PET/CT were calculated for (a) intra-abdominal extrahepatic recurrences, (b) extra-abdominal and/or hepatic recurrences and (c) all recurrences, and tumour marker levels were analysed.
Results: The sensitivity, specificity and overall accuracy of PET in detecting intra-abdominal extrahepatic CRC were 82%, 88% and 86%, respectively, compared with 88%, 94% and 92%, respectively, for PET/CT. The corresponding figures for detection of extra-abdominal and/or hepatic CRC were 74%, 88% and 85% for PET and 95%, 100% and 99% for PET/CT. Considering the entire population, the sensitivity, specificity and overall accuracy of PET were 80%, 69% and 75%, respectively, compared with 89%, 92% and 90%, respectively, for PET/CT. FDG-PET/CT examination correctly detected 40 out of a total of 45 patients with CRC. Two of five patients with falsely negative FDG-PET/CT findings had local microscopic recurrences and one had miliary liver metastases. Of 39 patients without CRC, three showed false positive FDG-PET/CT results. Two of these cases were due to increased accumulation in inflammatory foci in the bowel wall, while one was due to haemorrhaging into the adrenal gland.
Conclusion:FDG-PET/CT appears to be a very promising method for distinguishing a viable tumour from fibrous changes, thereby avoiding unnecessary laparotomy.(Votrubova et al.,2006)

4. Conclusion

The goal of any surveillance program should be detection of recurrent disease at a early time to allow subsequent curative therapy. Periodic clinical examinations, laboratory tests, radiographic imaging, and markers testing is necessary. The optimal combination and frequency of investigations in follow-up of patients after CRC resection has not been determined. It seems that intensive follow-up increased the re-resection rate for recurrent disease and improved overall survival but the survival advantage was not due to earlier detection of recurrence and cancer-related mortality was no better.
All patients having recurrences should be assessed by a multidisciplinary team in a cancer centre.

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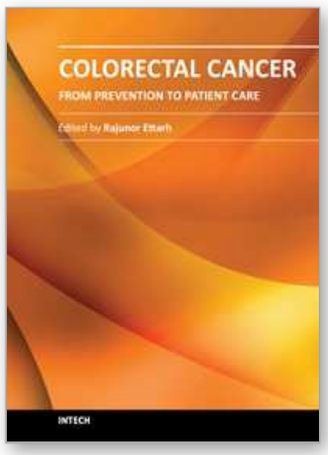
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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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