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COLORECTAL CARCINOMA – FOLLOW-UP

KOLOREKTALNI KARCINOM – »FOLLOW-UP«

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Kratak sadržaj: »Follow-up« protokoli se sprovode u celom svetu u cilju poboljšanja celokupnog efekta tretmana kolorektalnog kancera (CRC). »Follow-up« se istorijski razvijao sa drugim modalitetima tretmana CRC. U današnje vreme hirurgija je još uvek rizična da »second look« hirurgija za tretman pacijenata sa rekurentnim oboljenjem predstavlja udaljenu opciju. Imajući ovo u vidu, lako je da se zaključi da je »follow-up« u svojim počecima predstavljao samo istraživačku »alaktku« za razjašnjavanje prognoze posle sprovedene hirurgije. S obzirom da »efikasnost u troškovima« od skora dobija na značaju, kao i porast interesovanja za odgovarajuću distribuciju resursa, dolazi do povećanja u reevaluaciji »follow-up«. U cilju dizajna odgovarajućeg »follow-up« protokola neophodno ja da se definišu svi ciljevi i odrede prioriteti. Najvažniji i glavni cilj »follow-up«-a je poboljšanje preživljavanja. To se postiže na dva načina, detekcijom rekurencija bolesti ili postojanjem metahronog tumora. Drugi ciljevi »follow-up«-a su: menadžment posthirurških komplikacija, poboljšanjem kontakta pacijent-lekar i kvalitetom hirirškog ishoda. U odsustvu efikasnijih metoda tretmana, »follow-up« programi koji imaju za cilj ranu detekciju rekurencije su još uvek sporni, ali u pogledu kontrole i istraživačkih modaliteta se nastavlja sa njihovim postojanjem u budućnosti.

Ključne reči: kolorektalni karcinom, »follow-up«

Summary: Follow-up protocols are being conducted around the world in order to improve the overall effect of the colorectal cancer (CRC) treatment. Historically, follow-up developed together with other modalities of the CRC treatment. Still, in those days surgery was so hazardous that »second look« surgery for cure in patients with recurrent disease was too distant. Having that in mind, it's easy to conclude that the follow-up in its beginnings served only as a research tool to elucidate prognosis after surgery. In recent years, when cost- effectiveness gains its importance, and a question of proper distribution of recourses is being raised, follow-up programmes are reevaluated increasingly. In order to design the appropriate follow-up protocol, it's necessary to define all of the goals and set the priorities. Obviously, the main and the most important goal of the follow-up is to improve the survival. This is achieved in two ways, by detecting the recurrence of the disease or the existence of the metachronous tumor. Other goals of the follow-up are: management of the post surgical complications, improvement of the patient-doctor contact and quality control of the surgical outcome. In the absence of more effective treatment methods, follow-up programs aimed at early detection of the recurrence will have its debatable role, but as an audit and research modality, follow-up will continue to exist in the foreseeable future.

Key words: Colorectal carcinoma, follow-up

Follow-up protocols are being conducted around the world in order to improve the overall effect of the colorectal cancer (CRC) treatment.

Historically, follow-up developed together with other modalities of the CRC treatment.

The first major surgical attempts to cure a patient with CRC were made in early 20th century. Back in 1908, E. Miles described the first surgical procedure with the curative intent (1), which offered the patient some hope of the cure. Still, in those days surgery was so hazardous that »second look« surgery for cure in patients with recurrent disease was too distant. Having that in mind, it's easy to conclude that the follow-up in its beginnings served only as a research tool to elucidate prognosis after surgery. In that spirit, Cuthbert Dukes and Pearsy Lockhart-Mummery in the early 1920s began a programme of routine follow-up at St. Mark's Hospital. The aim of this enterprise was to correlate clinical and patohistological results, and this led to the well-known Dukes staging system for CRC. Afterwards, in the second half of the 20th century, first in the St. Mark's hospital and then in hospitals around the world, follow-up became a part of the routine treatment of the CRC. In recent years, when cost- effec-

tiveness gains its importance, and a question of proper distribution of recourses is being raised, follow-up programmes are reevaluated increasingly.

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Obviously, the main and the most important goal of the follow-up is to improve the survival. This is achieved in two ways, by detecting the recurrence of the disease or the existence of the metachronous tumor.

It is clear that the detection of metachronous malignancy in the early stage is practically the main aim of every follow-up regimen. Cali et al. (2) reported the calculated annual incidence of 0, 35% for the metachronous lesions, with cumulated incidence for 18 years of 6, 3%. Of course, these figures would be much higher if we were to add a number of premalignant lesions discovered.

Concerning the detection of recurrent disease, there is a wide spectrum of different opinions; still, results of many studies show the benefit of the follow-up. For example Ovaska and al. (3) showed that in the percentage of curative reoperations in the group of the patients with regular follow-up was 21%, compared with 7% in the group of patients with no follow-up.

Other goals of the follow-up are: management of the post surgical complications, improvement of the patient-doctor contact and quality control of the surgical outcome.

Post surgical complications are mainly related to wound problems, stoma care and deficits related to nerve damage during rectal surgery. These problems are usually resolved in the first year postoperatively and longer follow-up concerning these matters in not needed.

Concerning the stress of the knowledge to have malignancy together with all inconveniences that surgical treatment carries, patient-doctor contact is very important, but most frequently built on the individual basis. Some patients become too attached to the surgeon; others tend to »run away« from the whole episode.

Quality control of the surgical outcome gains its importance in the recent years. Important data concerning all aspects of the surgical work can be collected in this manner. Concerning rectal surgery, for example, different aspects of the postoperative quality of life can be investigated in this way and, generally, follow-up programme is ideal data source for national and international audits of surgical practice.

Some authors add to his list the process of deciding upon and delivering adjuvant therapy. As the results of many studies accumulate, this becomes another applicable reason for continuing doctor-patient contact after surgery. Furthermore, development of palliative chemoradiotherapy is another reason for early detection of the recurrence.

What diagnostic tools can we use in the follow-up, and what is theirs ideal combination with what frequency? Unfortunately, definitive answer to these questions is to be formulated in the near future, hopefully.

Still, we can mention the major elements of every follow-up.

– Physical examination, as a method of early detection of the recurrence, today, is quite unrewarding, and mainly can serve as a method of reassuring the patient and establishing better patient-doctor contact. Graham et al. for example, discovered that routine physical examination in the absence of symptoms, identified only 1% of the patients with the recurrent disease and none of them was amenable to potentially curative surgery (4). Concerning the interview with the patient, according to some is much more important than the physical examination alone. In a study conducted by Beart et al. 85% of recurrences were suspected based on patient symptoms (5).

– Occult blood test, has its role in detecting metachronous lesions in the early stage, in the same manner as in the screening programmes, but having in mind all other tests conducted during follow-up its role is somewhat limited.

– Proctosigmoidoscopy, important, inexpensive method, should be regularly conducted, especially if the anastomosis is within the reach of the instrument. It is important to state that 50% or more of metachronous lesions lie beyond the reach of the flexible sigmoidoscope.

– Colonoscopy, an examination that should be carried out postoperatively, as soon as possible in cases were colon couldn't be examined completely before the operation. Many studies show the high incidence of benign and malignant lesions in the remaining part of the colon (6). In studies were preoperative colonoscopy was performed, synchronous cancers were found in almost 8% (7) and 3 or more years afterwards, malignancies were discovered in an additional 8%. In study were colonoscopy after the operation, was performed annually (8) percentage of anastomotic recurrences, metachronous lesions and polyps was almost 5% combined all together, thus proving the importance of this method. Still, in cases of intraluminal recurrence, they are often discovered together with distant tumor deposits. Rodriguez-Bigas et al. (9) state that 90% of patients diagnosed with intraluminal recurrence, also demonstrated evidence of synchronous or distant tumor deposits at the time of diagnosis. The fact remains that by regular colonoscopic follow-up more than a third of patients will be diagnosed with the asymptomatic recurrence, and 75% of those will be amenable to potentially curative resection. (10)

– Barium enema can be conducted as a part of combined follow-up programme, still, with no clear advantage to the colonoscopy.

– Chest X-ray should be conducted annually, to discover the patient with pulmonary metastases, since there's a possibility for potentially curative pulmonary

resection and adjuvant therapy, but Beart and al. (5) discovered only 3% of patients with positive chest X-ray finding, none of them amenable to resection.

– Computed tomography (CT), is a widely accepted method in the follow-up. It is a good method for visualizing liver, retroperitoneum, pelvis and lung. Some authors even suggest performing baseline examination immediately after surgery and then perform the examination in intervals to detect recurrence of the disease in combination with other methods. For detecting liver metastases, CT appears to be optimal method, since Glover et al. (11) showed that CT and MRI were completely accurate in differentiating liver metastases from other lesions. Still, they also stated that only around 75% of the patients with liver metastases were identified.

– Magnetic resonance imaging (MRI), offers a better soft-tissue contrast than CT in the display of normal pelvic anatomy. Endorectal probes were developed to improve results in the discovering of the local recurrence; still the quality of the image can be degraded by the metal clips at the site of anastomosis. It is more accurate than CT in separating scar tissue from the recurrent tumor. NMR proved to have no advantages over CT in detecting liver metastases, but proved to be a method of choice for lesions of the central nervous system.

– Endorectal ultrasound (ERUS) proved its role in the preoperative staging of the rectal tumors. In the same way it can be used for the diagnosis of the local recurrence, especially in the early stage. It can also be used for ERUS guided needle biopsy of the tissue. For recurrent tumors with infiltration of adjacent organs, pelvic NMR is still preferable imaging method.

– Positron-emission tomography (PET) with F-florodeoxyglucose (FDG) is a method used to visualize intracellular biochemical processes. In this way it's possible to determine a tissue with increased metabolism of glucose. This is the case with tumor cells, and clear advantage of this method is its ability to recognize malignant tissue even where there are still no morphological changes. This method is very useful in cases were the difference between scar and tumor tissue cannot be seen using other imaging methods. Another important advantage of this method is a possibility to visualize entire body. FDG-PET scan is indicated in patients selected for curative reoperation. Valk et al (12) conducted a study were patients selected for curative surgery for CT diagnosed single recurrent tumor, were submitted to FDG-PET scan and additional lesions were seen in 32% of patients, and among 42 patients who eventually went to surgery, 35 had curative procedure. Downsides of this method are that lesions less than 1cm cannot be clearly visualized and some other inflammatory, infectious and granulomatous lesions can be seen as foci of increased FDG reuptake (13). FDG-PET scan has a number of well established indications: patients planned for curative reoperation, those with conflicting results of conventional imaging methods and patients with confirmed elevated CEA level and negative conventional tests.

– Tumor markers today are used in postoperative surveillance of patients who underwent potentially curative surgery and have risk for recurrence (14).

– The most common and well known marker for colorectal carcinoma is carcinoembryonic antigen (CEA). Back in 1965 Gold and Freedman demonstrated that elevated levels of serum CEA preceded clinical signs of the disease (15). Many studies have been conducted since to prove or disapprove that fact. Nowadays, many authors (16) state that CEA test is grossly insensitive in the diagnosis of the recurrent colorectal carcinoma. Moertel et al stated that only 25% percent of patients with symptomatic recurrent disease had abnormal levels of CEA (16). Shugarbaker et al had similar results (17). Still, general opinion concerning the CEA test is that the progressively high CEA levels are found in patients with more advanced disease (Dukes B2 and C) (18), a failure of elevated CEA levels after surgery are associated with poor prognosis and elevated levels of CEA usually precede clinical manifestation of the recurrence (19, 20).

Besides malignant diseases, elevated serum levels of CEA (>5 ng/ml) are found in a number of benign disorders. Smokers are known to have higher levels of CEA. A variety of benign liver disorders also can demonstrate higher levels of CEA, for example: hepatitis, cirrhosis, cholelithiasis, obstructive jaundice, cholangitis (21).

– CA 19-9 is a tumor marker used for colorectal carcinoma; still, studies (22) failed to demonstrate predictive value of this marker.

A number of new tumor markers are being developed. Some of them are: mRNA of tumor-specific antigen L6, CA 242, cytokeratines, TPA, TPS, TPA-M. The value of these markers, with a number of others is promising, but yet to be proved (23–27).

As we stated above, itžs relatively obvious that no single diagnostic method is optimal for all sites of the recurrent disease. Fiueredo et al. conducted systematic review of the literature regarding the impact of the follow-up on the survival rates of patients operated for colorectal cancer (28). The optimal follow-up program, according to the literature, should facilitate earliest possible detection of the recurrence as cost-effectively as possible. So, all procedures should be directed to the most common places of the recurrence. (*Table I*)

In several randomized trials, results of intensive and minimal program of follow-up were compared. Figuerdo et al. (28) revied four trials wich compred intensive to minimal follow-up, and two trials that compared intensive to conventional follow-up. As expected, overall survival was significantly improved for the patients in intensive follow-up programs. Yet, the number of recurrences was similar in both groups, but asymptomatic ones were more common in programs with intensive follow-up. In programs were CEA level measurements and liver imaging were used, survival was improved.

The improvement in patient survival in programs with intensive follow-up is achieved at the cost of fre-

Table I Sites of recurrent disease and screening tests for colorectal cancer.

Site of Recurrence	Patients with Recurrence at 5 Years by Site of Initial Tumour		Screening Tests
	Colon (%)	Rectum (%)	Diagnostic method
Liver	35	30	CEA, US or CT, RIS?, Sx, Chest X ray
Lung	20	30	Chest X ray, CEA, Sx
Peritoneal	20	20	CEA, Sx, CT, RIS?
Retroperitoneal	15	5	CEA, CT, RIS?, Sx
Peripheral lymph node	2	7	Physical exam, CEA
Others (brain, bones)	<5	<5	Sx, Scans
Loco-regional	15	35	CT pelvis, CEA, RIS?, Sx, endoscopy?, FOB?
Second or metachronous CRC	3	3	Colonoscopy, FOB?

Note: ?, questionable test; CEA, carcinoembrionic antigen; CT, computerized tomography; FOB, fecal occult blood; RIS, radioimmunoscintigraphy; Sx, symptoms; US, ultrasound (taken from Figueredo et al.)

quent, expensive tests. And one must keep in mind harmful consequences of those tests (29).

So the ideal follow-up program should be stratified, according to the risk of recurrence, affordable and easy to conduct.

Virgo et al. (30) compared 11 different strategies of follow-up in the USA. The main conclusion was that there was a wide range of cost (between $910 and $26717) without any indication that »higher cost strategies increase survival or quality of life«.

The differences among countries, regions even hospitals are great concerning follow-up programs; also in the literature we can find various recommendations (31).

We have devised our own follow-up program, based on our needs and experiences, and in concordance with basic follow-up rules. Patients are followed for 10 years postoperatively.

We have divided patients into two groups. First group, patents with low-risk from recurrence (Stage I and IIb) and other group, high-risk patients (Stage IIb and III).

The regimen for low-risk patients is as follows:

– Tumor markers (CEA, Ca 19-9) – every 3 months in the first year, every 6 months in the second, afterwards yearly.

– Abdominal ultrasound – every 6 months in the first year and once in the second, fifth and tenth year.

– Chest X-ray – every 6 moths in the first year and in the fifth year, also.

– Colonoscopy – yearly in the first tree years, afterwards every 3 years.

And the regimen for high-risk patients is as follows:

– Tumor markers (CEA, CA 19-9) – every 3 months in the firs year, every 6 moths in the second, than yearly.

– Abdominal ultrasound – every 6 month in the first 2 years, afterwards yearly Chest X-ray- yearly for the first 3 years

– Colonoscopy – yearly in the first 3 years afterwards once every 3 years.

To conclude, in the absence of more effective treatment methods, follow-up programs aimed at early detection of the recurrence will have its debatable role, but as an audit and research modality, follow-up will continue to exist in the foreseeable future.

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