Evidence-based follow-up in colorectal cancer—quo vadis?

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Summary Colorectal cancer is the third most common and the third most lethal cancer disease in the western world. As most patients undergo treatment with curative intent at initial diagnosis, postoperative surveillance protocols have been established with the primary aim to detect possible disease recurrence in an early resectable stage. Various international guidelines recommend an intensive surveillance protocol over a 5-year time period. These guidelines are based on the reported significant benefit regarding overall patient survival, and on the observation that 90% of recurrences occur within the first 5 years following resection. Surveillance protocols include regular clinical examinations, measurement of the carcinoembryonic antigen, computed tomography scans and regular endoscopies. While there is plenty of evidence regarding the scheduling of endoscopies, the frequency of carcinoembryonic antigen measurements and computed tomography scans has been ever since under debate. The benefit of intensive compared to low frequency surveillance protocols regarding disease-specific survival has never been shown. Moreover, recent meta-analyses and randomized controlled trials challenge current guidelines. Intensive carcinoembryonic antigen assessment and computed tomography scan follow-up protocols seem to fail in generating better overall and disease-specific survival in colorectal cancer patients compared to less intensive surveillance strategies. This change over the last few decades

parallels the treatment evolution of colorectal cancer from a primarily surgical to a multidisciplinary task. Instead of advocating a reduction of the follow-up intensity, these findings should stimulate the colorectal oncology field to move from a one-fits-all to a patient-centered surveillance.

Keywords Colorectal cancer · Surveillance · Follow-up · Guidelines · CEA · Tumor marker · Recurrence

Introduction

Colorectal cancer (CRC) represents with an overall life time risk of 4.15% in women and 4.49% in men the third most common cancer diagnosed in the western world. Despite the fact that most of the diagnosed cancers can be detected in early stages and can be therefore treated with curative intent, it is the third leading cause of cancer-related deaths [1]. Advances in diagnostic tools, surgical techniques, neoadjuvant and adjuvant systemic treatments combined in multidisciplinary approaches have broadened the indication for curative intended treatment strategies. As a matter of fact, the risk of disease recurrence increased by up to 40% at the time of treatment because more patients with advanced stages undergo successful curative treatment; the majority of recurrences occur within the first 3 to 5 years [2]. Disease recurrence might manifest itself as locoregional recurrence, distal metastasis or as a metachronous colorectal primary.

Detecting the recurrent disease in an early, resectable stage with the aim to achieve a survival improvement is the major goal of postoperative CRC surveillance protocols. In addition, curative treatment approaches by implementation of multimodal strategies in patients presenting with liver-limited or lung-limited distant metastasis (in both cases >40% 5-year

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survival) justify postoperative surveillance protocols for CRC [3, 4].

Other not less important goals include issues like identification of precancerous lesions which might represent precursors of metachronous CRC, diagnosis of surgery-related problems (e.g. incisional hernia, anastomotic stenosis), psycho-oncological support and last but not least audit of one's own center's data and potential impact of new therapeutic approaches [5].

Based on the observation that 90% of recurrences will occur within the first 3 to 5 years after treatment, major cancer societies like ESMO (European Society for Medical Oncology), ASCO (American Society of Clinical Oncology), NCCN (National Comprehensive Cancer Network) as well as the Austrian Society for Surgical Oncology (ACO ASSO) recommend 5-year surveillance for CRC [6]. All the protocols resemble an intensive surveillance strategy built on four pillars: clinical examination, carcinoembryonic antigen (CEA), computed tomography (CT scans) and endoscopies performed at regular intervals.

The common intensive surveillance strategy relies on different meta-analyses and systematic reviews which showed that this strategy was associated with a better overall survival of patients following surgery for non-metastatic CRC compared to less intensive protocols [7–9]. However, many of the corresponding studies are outdated and have different shortcomings (e.g. small number of patients). A couple of recent methodologically high-quality trials have been published with consistent results showing that the expected survival benefit due to earlier detection of recurrence has not been achieved in intensive surveillance protocols. The various reduced frequency follow-up regimes analyzed by the most representative trials (COLOFOL study, GILDA study and FACS study) consisted of CT and CEA at 12 and 36 months, CEA only, CT only, CEA and CT, or symptom-based follow-up [10–12]. The observation that the benefit of early detection of recurrence after curative treatment of CRC does not translate into improved cancer-specific survival definitely challenge current guidelines.

Clinical examination

Clinical examination, including recent medical history, is a routine procedure in every out-patient clinic regardless of the patients' diseases. In CRC surveillance its role can be considered marginal regarding diagnosis of asymptomatic recurrences, and it might be even less in rectal cancer patients where radiation therapy does not allow any differential diagnosis between local recurrence and radiation consequences [13]. In this context, it should be mentioned that there is no evidence for performing regular fecal occult blood tests (FBOT).

The usefulness of regular examinations has to be seen in the possibility to address surgery-related prob-

lems, psychological and psychosocial issues [14] and also in the better adherence to the surveillance protocol if hospitals offer dedicated outpatient clinics for CRC [15].

Carcinoembryonic antigen

The carcinoembryonic antigen (CEA) is an oncofetal antigen produced by epithelial tumor cells in the digestive tract. In general, measurement of the tumor marker CEA is recommended every 3–6 months for 5 years [6]. It represents a cheap and safe test for the follow-up of colorectal cancer patients [16].

Elevated postoperative CEA is associated with a high probability of disease recurrence; however, negative CEA does not exclude tumor recurrence [17]. In fact, up to 40% of all recurrences of colorectal cancer do not have an accompanying increase of CEA [18]. The sensitivity of CEA testing ranges from 17 to 100%, while the specificity ranges from 66 to 98% in different studies [16]. A major disadvantage of CEA is the high rate of false positives (e.g. cigarette smoking), and there are also no clear data that confirm a significant impact on survival if assessed more frequently [16, 19]. Recently, a large randomized study showed that CEA screening provides an increased rate of surgical resection of recurrence compared with minimal follow-up. However, a survival advantage was not observed [10].

Imaging—computed tomography scan

The computed tomography (CT) scan is the imaging tool of choice in follow-up of CRC. Most guidelines recommend CT scans every 6–12 months for 3 or 5 years. However, the optimal frequency of CT imaging is not clear. Frequent use does not seem to be superior to less frequent use [11]. Ultrasound has a low sensitivity, magnetic resonance imaging is rather limited to the examination of the liver, positron emission tomography is indicated only in special cases, and endosonography may help only to detect local recurrence in rectal cancer. The major advantage of CT scans of the pelvis, abdomen and thorax is the early diagnosis of asymptomatic distant recurrence, which may still be resected with curative intent, especially in liver and lung [6, 20]. The FACS randomized clinical trial has shown that both CT and CEA were associated with an elevated rate of surgical treatment of recurrence, however, with no survival advantage. Interestingly the combination of CT and CEA did not seem to be superior to either alone [10].

Some experts argue that CT is associated with a relevant radiation exposure and a risk of new malignancies. Alternatively, chest x-ray and abdominal ultrasound can be performed to detect liver or lung metastases; an ongoing French study will provide further clarity about whether this combination is equal to CT alone [21].

Endoscopy

In contrast to CEA measurement and CT scans, there is less contradictory evidence for the performance of surveillance endoscopies to diagnose synchronous and metachronous CRC as well as intraluminal recurrences. Considering the reported prevalence of up to 7% of synchronous CRC [22] preoperative colonoscopy in non-obstructive disease is mandatory. The high incidence of metachronous diseases within the first year in older studies as well as retrospective collected data reflect probably overlooked lesions at the time of initial CRC diagnosis and emphasize even more the importance of preoperative endoscopy [23]. It is generally recommended to perform the first colonoscopy within the first 3 to 6 months following surgery if preoperative colonoscopy was not possible [24].

While the recurrence risk decreases over time the estimated cumulative incidence of metachronous CRC persist with 0.35% per year following curative CRC resection [22]. This is the basis for recommending the first colonoscopy one year following CRC resection (or one year following early postoperative colonoscopy in initial obstructive disease), and in case of normal findings 3 years afterwards. The interval should be shortened in case of abnormal findings like dysplastic adenomas. After completed surveillance, colonoscopies should be repeated at regular intervals according to the national CRC screening protocols [24].

Additional aspects

It has to be highlighted that current international guidelines are based on data of patients operated on UICC stage II and III CRC. The expert guidelines do not particularly consider UICC stage I and IV because consistent data are missing. Over 95% of patients with UICC stage I are cured with surgery and do not need adjuvant chemotherapy. Consequently, the recurrence rate is minimal and intensive surveillance seems to be dispensable. In patients with UICC stage IV with an obvious high risk of recurrence of metastases, studies have demonstrated on the contrary that intensive 3-monthly surveillance with CT after hepatic resection is reasonable and improves outcome [25]. Similarly, patients with hereditary syndromes (e.g. Lynch syndrome) also need more frequent surveillance to detect recurrence and additional tumor manifestations [26]. The follow-up of patients with rectal cancer has become particularly challenging because of new treatment options emerging recently. Local T1 tumor resection or watch and wait concepts demand an intensive follow-up approach (e.g. endoscopy every 3 months for 2 years) until representative data about less intensive surveillance are published.

Conclusion

Recent trials and meta-analyses challenge current CRC surveillance guidelines. Intensive approaches to surveillance are expensive, but facilitate early detection of recurrence after curative treatment of colorectal cancer. On the other hand, this benefit and less intensive approaches to surveillance do not seem to

Table 1 Follow-up protocol of colorectal cancer patients at the Department of Visceral, Transplant and Thoracic Surgery at the Medical University of Innsbruck based on American NCCN

	Months	1st year				2nd year				3rd year				4th year				5th year			
		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Colon Carcino-	CEA	x	x	x	x	x	x	x	x	—	x	—	x	—	x	—	x	—	x	—	x
	Clinical Examination	x	x	x	x	x	x	x	x	—	x	—	x	—	x	—	x	—	x	—	x
	Colonoscopy	(x ^a)	—	—	x	—	—	—	—	—	—	—	—	—	—	—	x ^b	—	—	—	—
	CT scan	—	—	—	x	—	—	—	x	—	—	—	x	—	—	—	x	—	—	—	x
Rectal Carcino-	CEA	x	x	x	x	x	x	x	x	—	x	—	x	—	x	—	x	—	x	—	x
	Clinical Examination	x	x	x	x	x	x	x	x	—	x	—	x	—	x	—	x	—	x	—	x
	Colonoscopy	(x ^a)	—	—	x	—	—	—	—	—	—	—	—	—	—	—	x ^b	—	—	—	—
	CT scan	—	(x ^c)	—	x	—	(x ^c)	—	x	—	—	—	x	—	—	—	x	—	—	—	x
	Rectoscopy ^d	x	x	x	—	x	x	x	x	—	x	—	x	—	x	—	—	—	x	—	x

In case of curative treatment of distant metastases, CT scans are repeated in 6-monthly intervals during the first 2 years and the surveillance period is prolonged for further 5 years

CEA carcinoembryonic antigen, CT computed tomography

^aIf not performed preoperatively

^bIf normal findings to be repeated regularly according to national screening protocols

^cIn high-risk patients (G III, L pos, V pos)

^dIn case of local excision or “watch & wait” strategy

Guidelines, European ESMO Guidelines and Austrian ACO-ASSO Guidelines

be inferior. However, the current recommendation is still an intensive surveillance protocol over a 5-year time period (Table 1). Reduced-frequency surveillance protocols should only be offered in the setting of clinical trials.

Rather than encouraging a reduction of postoperative surveillance examinations the ongoing controversy should stimulate further evolution of patient-centered and stage-adapted surveillance protocols in the light of increasing knowledge of molecular, immunological and microbioma-associated aspects known to influence patients' outcome.

Take-home message

Current guidelines recommend intensive surveillance postoperative protocols based on regular clinical examinations, measurements of CEA, CT scans and endoscopies. Recent data challenge these surveillance protocols and call for more patient-centered and stage-adapted protocols.

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Conflict of interest M. Maglione and A. Perathoner declare that they have no competing interests.

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