Screening and Surveillance Colonoscopy

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1. Introduction

Colorectal cancer (CRC) is the second most frequent malignant disease in Europe. Every year, 412,000 people are diagnosed with this condition, and 207,000 patients die of it. Secondary prevention of CRC consists of early diagnosis of the disease in asymptomatic individuals (screening) and long term follow up of high risk patients (surveillance). Three groups of screening methods are currently available: stool testing (guaiac or immunochemical fecal occult blood tests – gFOBT and FIT respectively and DNA tests), endoscopic examinations (flexible sigmoidoscopy and colonoscopy) and radiologic examinations (computed tomographic colonography and double contrast barium enema). Colonoscopy is therefore used as the only screening method or as a second step in case of positive results of primary screening examination (two steps screening programs). From 27 countries in the European Union, the most frequently used test is FOBT (in 11 states). There is a choice between FOBT and colonoscopy in 6 countries. FOBT and flexible sigmoidoscopy is available in Italy. Currently, the only country using colonoscopy as the only screening method is Poland. At the end of 2010, the European guidelines for quality assurance in colorectal cancer screening and diagnosis were published, summarizing the evidence based medicine data for the efficacy, the interval, the age range, the risk-benefit and cost-effectiveness of colonoscopy screening. Unfortunately, prospective randomized trial on the effect of screening colonoscopy in the reduction of CRC incidence and mortality has not been published yet. Promising should be the NordICC study, which was introduced in 2009, however the results will be available in a fifteen year period. Series of recently published studies (Canada, Germany, Poland) focusing on the interval (post-colonoscopic) cancers confirmed the inadequate protection of proximal colon by colonoscopy. Another important issue would be the quality and safety of colonoscopy and the bowel cleansing. Concerning the surveillance colonoscopy, it plays a major role in specific follow up strategies in CRC high risk groups. It can be concluded that with some limitations, colonoscopy still remains the fundamental diagnostic and prophylactic examination in colorectal cancer screening and surveillance.

2. Colorectal cancer epidemiology in Europe

Colorectal cancer is the second most frequent malignant disease in developed countries. CRC incidence is generally higher in male population, and the risk of the disease increases

with age, as the majority of cases are diagnosed in patients over 50 years of age (Spann et al., 2002). Burden of European countries is ranked as the highest in the global statistics, both in incidence and mortality. Compared to the US, in 1998 – 2002 the European population showed a similar incidence for men, while that for women was slightly lower; the incidence in the USA for men and women was 38.6 and 28.3 respectively: in Europe it was 38.5 and 24.6 (ASR-W), as calculated per 100,000 inhabitants (Curado et al., 2007) . However, mortality over the same period of time was significantly higher in Europe than in the US, both for men and women: in the USA the figures were 13.5 and 9.2 respectively, while in Europe they were 18.5 and 10.7 (ASR-W), as calculated per 100,000 inhabitants (World Health Organization [WHO], 2006). To document the situation in Europe, we used figures available from the international studies summarizing global and European epidemiologic data (Curado et al., 2007; Ferlay et al., 2004, 2007; Parkin et al., 2005). A detailed comparison of countries within Europe using the global age standardization (ASR-W) of incidence is presented in figure 1.

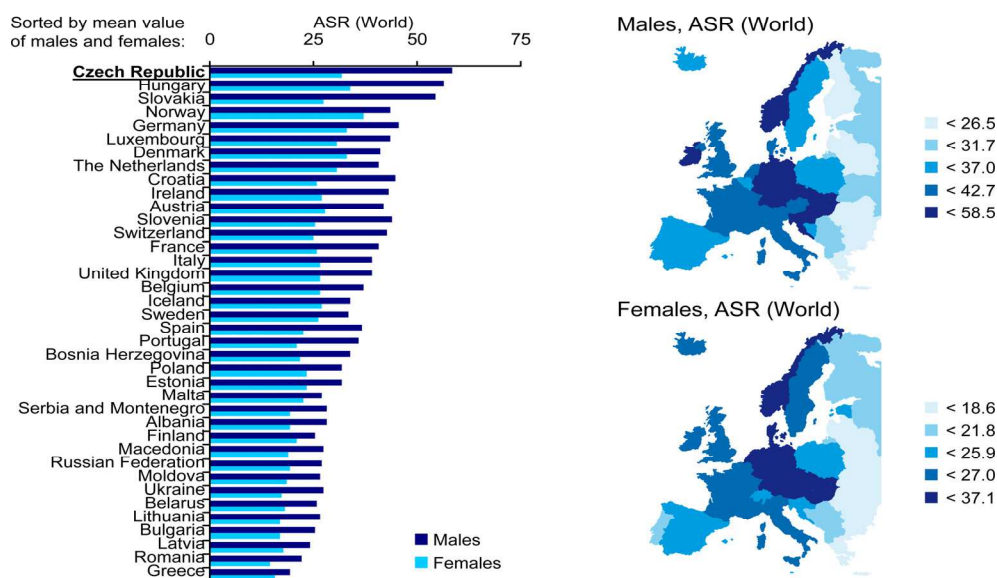Incidence in international comparison – European countries

Fig. 1. International comparison of CRC incidence in European countries

Colorectal cancer comprises 12.9% of all newly-diagnosed carcinomas in the European population (men 12.8%, women 13.1%) and account for 12.2% of deaths caused by malignancy. Colorectal cancer is the second most common malignancy, after breast carcinoma (13.5% of all malignities), followed by bronchogenic carcinoma (12.1% of all malignancies). Every year 412,900 people are diagnosed with CRC in Europe, and 207,400 of them die of the disease (Ferlay et al., 2007). The average incidence has shown a tendency to rise in recent years, with an annual increment 0.5%. Data available regarding time trends of CRC mortality are displayed in figure 2. The CRC-related mortality has stabilized or shown a slight decrease over recent years.

Mortality trends of colorectal cancer in Europe
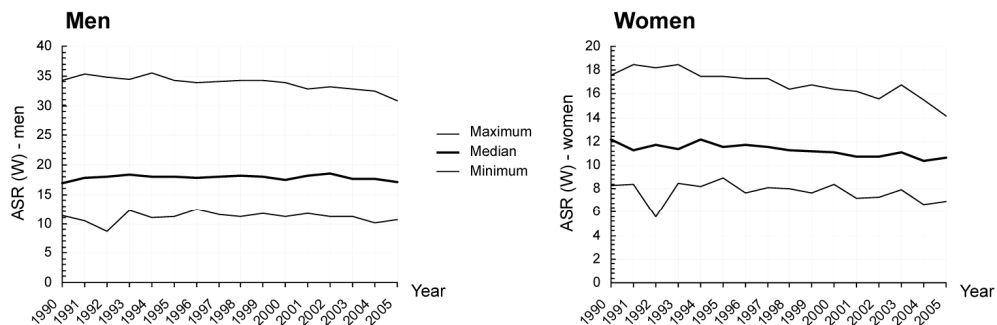
Data sources:
World Health Organization, mortality database http://www.who.int/whosis/whosis/ (accessed on 11/09/2008)
United Nations, World Population Prospects, the 2006 revision http://www.un.org/esa/population/unpop.htm

As available in WHO database, countries with cancer registry (Cancer Incidence in Five Continents, Vol. IX)

Fig. 2. Colorectal cancer mortality trends in Europe (men left, women right)

3. Colorectal cancer prevention

Colorectal cancer belongs to preventable cancers. Primary prevention focuses on dietary and lifestyle recommendations. Secondary prevention of CRC consists of early diagnosis of the disease in asymptomatic individuals (screening) in patients older than 50 years of age and a long term follow up of high risk patients (surveillance).

4. Colorectal cancer screening

Three groups of screening methods are currently available (see in the table below): stool testing (guaiac or immunochemical fecal occult blood tests – gFOBT and FIT respectively and DNA tests), endoscopic examinations (flexible sigmoidoscopy and colonoscopy) and radiologic examinations (computed tomographic colonography and double contrast barium enema). Colonoscopy is therefore used as the only screening method or as a second step in case of positive results of primary screening examination (Zavoral et al, 2009).

Type of method	Method
Stool tests	for presence of occult blood
	guaiac-based (gFOBT)
	immunochemical (FIT)
	for presence of abnormal DNA
Endoscopic examinations	flexible sigmoideoscopy (FS)
	colonoscopy
Radiologic examinations	computed tomographic colonography (CTC)
	double contrast barium enema (DCBE)

Table 1. Overview of CRC screening methods

In 2008, the Report on the Implementation of the Council Recommendation on Cancer Screening, which provides the most comprehensive data available, was published (Karsa et al., 2008). According to this report, CRC screening is running or being established in 19 of 27 EU countries. The target group contains approximately 136 million individuals suitable for CRC screening (aged 50 to 74 years). Of this number, 43% individuals come from 12 countries where CRC population screening is performed or being prepared on either national or regional levels; 34% come from 5 countries where national population screening has been implemented (Finland, France, Italy, Poland, and United Kingdom). In 7 EU countries, national non-population based screening is carried out, which covers 27% of the target population. In 2007, gFOBT (which was the only test recommended by the Council of the European Union in 2003) was used as the only screening method in twelve countries (Bulgaria, Czech Republic, Finland, France, Hungary, Latvia, Portugal, Romania, Slovenia, Spain, Sweden, and United Kingdom). Colonoscopy was the only screening method used in Poland. In six countries, two types of tests were used: iFOBT and FS in Italy, and gFOBT and colonoscopy in Austria, Cyprus, Germany, Greece, and Slovak Republic. In the remaining eight states (Belgium, Denmark, Estonia, Ireland, Lithuania, Luxembourg, Malta, and the Netherlands), CRC screening has not been implemented yet. The age limit for the target population varies across the EU countries. In 2007, it was estimated that a total of 12 million individuals participated in CRC screening.

4.1 Selected colonoscopy CRC screening programs

Poland is currently the only state using colonoscopy as the only screening method, without the alternative of FOBT. An opportunistic screening programme was initiated in 2000, and by now, this had grown to 80 centers across the whole of Poland. The programme is financed by the Ministry of Health, independentanly from the overall healthcare system. The target population (asymptomatic individuals aged 55–66 years) is recruited through general practitioners. High emphasis is placed on the quality control of colonoscopies, with complications reported for 0.1% procedures, and no patient dying. The advantage of the programme consists in thorough monitoring and evaluation, including monitoring of interval cancers (Regula et al., 2006).

Germany was the first country to introduce a population screening programme (in 1976) based on an annual gFOBT for individuals older than 44 years of age. Starting in 2002, the participants were offered a choice between colonoscopy at 55 years of age (in a ten-year interval) and FOBT in annual intervals between 50 and 54 years of age and in a two-year interval after 55 years of age. In case of FOBT positivity, screening colonoscopy followed. Between 2003 – 2008, there were 2 821 392 colonoscopies performed in over 2 100 practices all over Germany. The cumulative participation rate was 17.2% for women and 15.5% for men. Adenomas were diagnosed in a total of 19.4%, advanced adenomas in 6.4% and carcinomas in 0.9% of the examined patients. The majority of cancers were in early stage (UICC 47.3%, UICC II 22.3%, UICC III 20.7%, and UICC IV 9.6%). The overall and serious complication rate was 2.8 and 0.58 respectively per 1 000 colonoscopies. The cost analyses have proven the cost effectiveness of such screening (Pox et al., 2007).

In the Czech Republic, CRC screening has many years of tradition. It was the second country in the world to start a nation-wide screening programme (in 2000), based on biennial gFOBT offered to asymptomatic individuals older than 50 years of age. In order to achieve higher compliance rate, screening colonoscopy was added to current FOBT

screening as an alternative method in 2009, in the same intervals as in the German programme. Both, gFOBT and various types of FIT are offered as well. During years 2006 – 2010, there were 47 760 screening colonoscopies (FOBT+) and 5 574 primary screening colonoscopies performed. Adenomas and carcinomas were diagnosed in 16 454 (30.9%) and 2 539 (4.8%) respectively. The proportion of advanced adenomas and generalized cancer (UICC stage III and IV) was 48% and 20.7% respectively (Zavoral et al., 2009).

4.2 Screening colonoscopy studies

The multinational NordICC (The Nordic-European Initiative on Colorectal Cancer) study was introduced in June 2009, however the results will be available in a fifteen year period. This study focuses on monitoring the effect of colonoscopy screening on reducing CRC incidence and mortality. The northern states of Europe (Norway, Sweden, and Iceland), Poland, and the Netherlands all participate. The Czech Republic, Hungary and Latvia are currently observers and may join the study later. According to the study protocol, a minimum of 66,000 individuals aged 55 to 64 years will be drawn directly from population registers in the participating countries and randomly assigned to either once-only colonoscopy screening or no screening (2:1 randomization, men and women). The primary objective is to compare the incidence and mortality against the control group after 15 years. At this time, more than 5 500 individuals have been examined so far and the recruitment will continue until the end of 2012 (NordiCC Study Protocol, 2011).

CONFIRM (Colonoscopy vs. Fecal Immunochemical Test Reducing Mortality from Colorectal Cancer), the VA Cooperative study, is a multicenter, randomized, parallel group trial directly comparing screening colonoscopy with annual FIT screening in average risk individuals. The quantitative FIT (OC Sensor Diana) cut-off will be set at 100 ng/ml. The primary endpoint expected is CRC mortality reduction by 40% within a 10 year enrolment. The planned study duration is 12.5 years with 2.5 years of recruitment of 50 000 participants (1:1 randomization, 95% men, aged 50 – 75) and 2.5 years of follow-up for enrolled participants (Dominitz et al., 2011).

COLONPREV (Colorectal Cancer Screening in Average-Risk Population: a Multicenter, Randomized Controlled Trial Comparing Immunochemical Fecal Occult Blood Testing versus Colonoscopy) study is being carried out since November 2008 in eight Spanish regions under the coordination of the public health system, primary care physicians and tertiary academic medical centers. Asymptomatic individuals aged 50 – 69 years have been randomized into two groups (1:1). Biennial quantitative FIT (OC Sensor, cut-off level 75 ng/ml), followed by colonoscopy in case of its positivity has been offered to one group and colonoscopy to the second group. First preliminary results are expected in June 2011 (Castellas et al., 2011)

The Japan Polyp Study (JPS) is a multicenter randomized control trial focusing on postpolypectomy surveillance and conducted in eleven centers since February 2003. Two complete colonoscopies with the removal of all neoplastic lesions (to reach "clean colon") have been performed to the enrolled patients who have been randomized into two groups (1:1) afterwards, according to the colonoscopy follow-up interval. One group underwent a colonoscopy after 48 months, the second group at 24 and 48 months. From a total of 4 752 individuals, 3 926 (83%) agreed with the initial colonoscopy and 2 757 (58%) patients were randomized. There has been a great impact on polyp distribution and macroscopic type in the first two initial colonoscopies. Very high adenoma detection (63%) was reached (Matsuda, 2011).

4.3 Screening colonoscopy characteristics

At the end of 2010, the European guidelines for quality assurance in colorectal cancer screening and diagnosis were published, summarizing the evidence based medicine data for the efficacy, the interval, the age range, the risk-benefit and cost-effectiveness of colorectal cancer screening, including sigmoidoscopy (FS) and colonoscopy screening analysis.

4.3.1 Evidence for effectiveness of sigmoidoscopy screening

Flexible sigmoidoscopy screening reduces colorectal cancer (CRC) incidence and mortality if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the outcomes, adverse effects and costs (Atkin et al., 2010). The evidence on the efficacy is avaible from randomised controlled trials (RCTs). The most important one is the large UK study in which 57 237 individuals were randomised into the screening group for a once-only sigmoidoscopy alone. This study found a significant 31% reduction in CRC mortality and also a significant reduction in CRC incidence from sigmoidoscopy in an intention-to-treat analysis (Atkin et al., 2010).

The optimal interval for sigmoidoscopy screening was only assessed in two indirect studies that only considered intervals of three and five years (Platell et al., 2002, Schoen et al., 2003). The UK flexible sigmoidoscopy screening study showed that there was little attenuation of the protective effect of sigmoidoscopy after 11 years of follow-up. This is in line with the evidence for colonoscopy screening. In conclusion, the optimal interval for endoscopy screening should not be less than 10 years and may even be extended to 20 years (Atkin et al., 2010).

There is limited evidence suggesting that the best age range for flexible sigmoidoscopy screening should be between 55 and 64 years (Segnan et al., 2007). One study demonstrated that elderly subjects (75 years old) have an increased rate of endoscopist-reported difficulties and a higher rate of incomplete examinations compared to subjects aged 50–74 years (Pabby et al, 2005). Average-risk sigmoidoscopy screening should be discontinued after 74 years of age, given the increasing co-morbidity in this age range (Atkin et al., 2010).

4.3.2 Evidence for effectiveness of colonoscopy screening

Limited evidence exists on the efficacy of colonoscopy screening on CRC incidence and mortality (Atkin et al, 2010). However, two recent case–control studies found a significant reduction of 31% in CRC mortality (Baxter et al., 2009) and 48% in advanced neoplasia detection rates (Brenner et al., 2010). The reduction in these studies was limited to the rectum and left side of the colon. No significant reduction was found in right-sided disease. Cross-sectional surveys have shown that colonoscopy is more sensitive than sigmoidoscopy in detecting adenomas and cancers and that this increased sensitivity could translate into increased effectiveness (Walsh et al., 2003). The efficacy of colonoscopy as a primary screening test has not been proven by prospective randomized control trial.

The optimal interval for colonoscopy screening has been assessed in a cohort study and a case-control study. The cohort study found that CRC incidence in a population with negative colonoscopy was 31% lower than general population rates and remained reduced beyond 10 years after the negative colonoscopy (Singh et al., 2006). Similar results were obtained in the case–control study (Brenner et al., 2006) where the reduction of risk of CRC was 74 % and persisted up to 20 years.

Screening colonoscopies do not need to be performed at intervals shorter than 10 years and this time interval may even be extended to 20 years (Atkin et al., 2010).

There is no direct evidence confirming the optimal age range for colonoscopy screening. Indirect evidence suggests that the prevalence of neoplastic lesions in the younger population (less than 50 years) is too low to justify colonoscopic screening, while in the elderly population (more than 75 years) the lack of benefit could be a major issue (Pabby et al., 2005). The optimal age for a single colonoscopy appears to be around 55 years. Average risk colonoscopy screening should not be performed before age 50 and should be discontinued after 74 years of age (Atkin et al., 2010).

## 5. Colonoscopic surveillance following adenoma removal

The adenomatous polyp is the precursor of most colorectal cancers and is the most frequently detected lesion during a colonoscopy examination (Lieberman et al., 2000). Hyperplastic polyps, on the other hand, usually have no clinical significance. Based on the statistics, in 33 % – 50 % of patients consecutive adenomas develop within three years after the removal of first adenoma. In addition, in 0,3-0,9 % of cases colorectal carcinoma is detected within five years (Alberts et al., 2000; Arber et al., 2006; Baron et al., 2006; Martinez et al., 2009; Robertson et al., 2005). Most of these adenomas and malignancies are, however, represented by lesions missed during the first colonoscopy. The quality of a colonoscopic examination must therefore be emphasized. Medical centers involved in screening programmes thus often undergo quality controls. One of the key aims of a surveillance colonoscopy is to detect all new lesions or lesions that have been missed at baseline colonoscopy before they progress to malignancy. The other aim of a follow-up colonoscopy is the detection of colorectal carcinoma at an early, prognostically more favorable stage (Robertson et al., 2005).
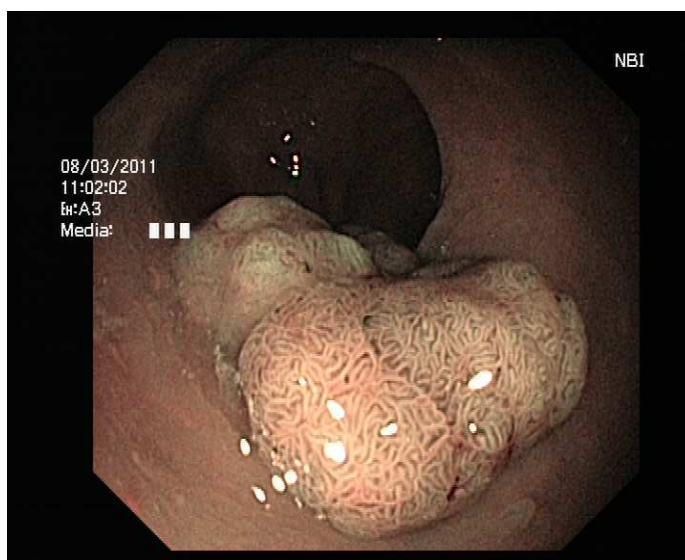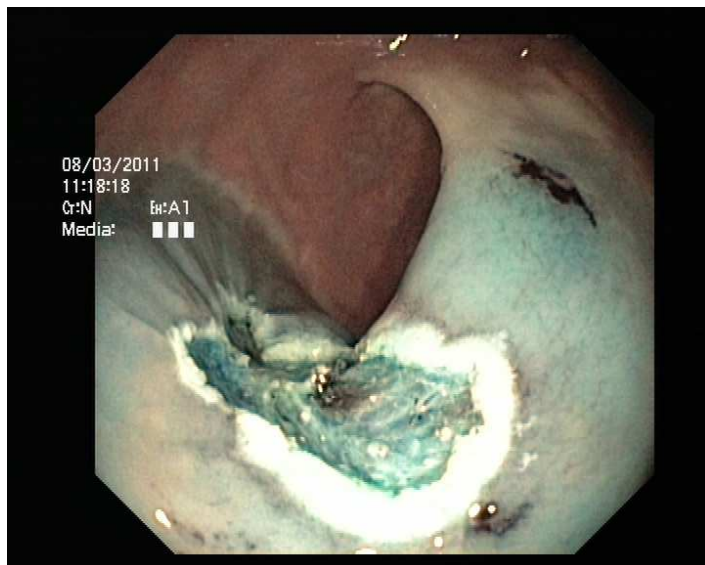

Picture 1. Sessile polyp - white light
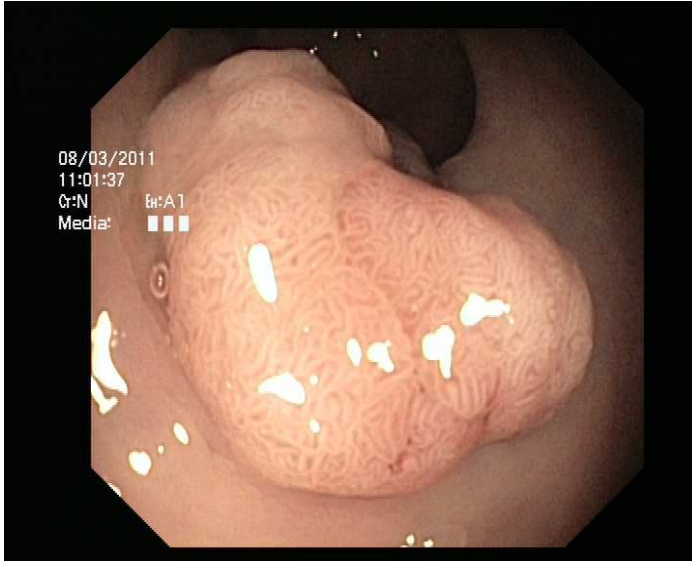
Picture 2. Sessile polyp - NBI (narrow band imaging)
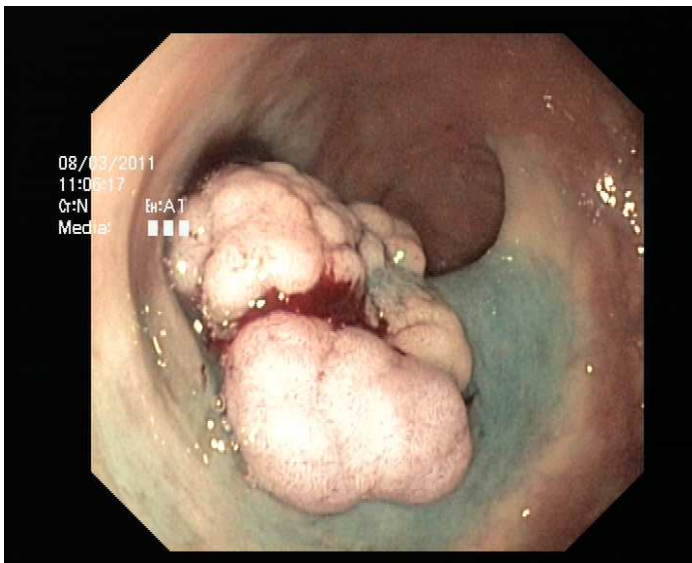
Picture 3. Sessile polyp - Patent Blue injection

Picture 4. Postpolypectomy site

Colonoscopy is an invasive method with a small, however not insignificant risk of possible complications, amongst which are perforation (0,06 % diagnostic and 2 % therapeutical colonoscopies) and hemorrhage after polypectomy (02,-2,7 % according to size of lesion) (Rosen et al., 1993). Surveillance colonoscopies represent a burden for endoscopic centers prolonging the waiting lists. For these reasons, surveillance colonoscopies should be carried out in recommended intervals in order to prevent the development of colorectal carcinoma. The malignant potential of an adenoma depends on its size, histological verification and the grade of dysplasia. It is higher in advanced adenomas (larger than 10 mm or more, with a villous component or a high grade dysplasia). Recent studies show, that the villous component is a less significant predictor for the development of malignancy than the remaining two factors.

5.1 Risk factors for advanced adenomas and colorectal cancer after baseline polypectomy

The risk of detection of advanced adenoma or carcinoma during a surveillance colonoscopy depends on the quality of the first (baseline) colonoscopy and the characteristics of the removed polyp.

It is generally agreed that high quality colonoscopies carried out less frequently are more efficient in the prevention of colorectal cancer than more frequent colonoscopies of a lower quality. Colonoscopy examination should only be carried out after adequate bowel preparation in order to properly visualize bowel mucosa. Patients with poor bowel preparation have to be invited for a repeated colonoscopy, considering the colonoscopy was well indicated in the first place. The examination must also be complete (reaching the caecum) and the withdrawal of an endoscope should be slow and careful. All detected lesions have to be removed carefully, ideally as hoc during their detection since they can

easily be overlooked during the next examination. Polyp removal must be done during the withdrawal of a scope due to the possible risk of bleeding and perforation.

Based on the following meta-analysis (Saini et al., 2006) it is obvious that a personal history of 3 adenomatous polyps increases the risk for the presence of advanced adenoma 2x, whereas the history of five polyps increases the risk at a surveillance colonoscopy 4x, as opposed to the detection of a single polyp during a baseline colonoscopy. The polyp size also plays a significant role. The real size is considered to be the size of the histological specimen measured by a pathologist. In case a piece-meal polypectomy is performed, the size is based upon the judgment of the endoscopist (comparing the lesion with a known size of biopsy forceps). Adenomas measuring between 10 to 20 mm have twice the increased risk, adenomas measuring 20 mm or more have 3x the increased risk of turning to malignancy as opposed to small adenomas (up to 10mm) (Cafferty et al., 2007).

Adenoma histology does not play as significant role as believed earlier. However, a villous structure polyp increases the chance of villous adenoma detection during a surveillance colonoscopy (Cafferty et al., 2007). On the other hand, the presence of high grade dysplasia significantly increases the risk of malignant changes in adenomas of varying size (Saini et al., 2006).

Based on the studies listed below, the localization of polyp in the right colon increases the risk of advanced colorectal neoplasia 1,5-2,5 times as opposed to its localization in the left colon (Laiyemo et al., 2009; Martinez et al., 2009; Saini et al., 2006)

5.2 Risk factors in patients

One of the risk factors is older age, which correlates with the higher incidence of advanced colorectal neoplasia, at the same time it is related to an increased difficulty of a colonoscopy examination and its performance, worse bowel preparation and a higher risk of complications related to the examination itself. It is always necessary to proceed individually recognizing all comorbidities of a patient, the benefit of the examination itself, whilst considering whether the lead time for progression of adenoma to colorectal cancer does not exceed the life-expectancy of an individual, particularly in patients aged 75 years or older. The upper age boundary for surveillance cessation is usually 75 years of age. A positive family history for an adenoma, unless a dominant genetic disease is suspected, does not require any special precautions during surveillance colonoscopies (Atkin et al., 2010).

5.3 Stratification of risk factors in patients

According to European guidelines for the quality assurance in colorectal cancer screening and diagnosis (2010), the degree of risk should be determined based on the findings at baseline colonoscopy. It is recommended to divide patients into groups with low, intermediate and high risk of colorectal neoplasia development, thus more easily determining the interval of colonoscopy examinations. Based on these results, further surveillance can be modified (Atkin et al., 2010).

Low risk group: Patients with one or two polyps measuring up to 10 mm, with tubular structure and low grade dysplasia are considered to be in low risk of developing colorectal carcinoma and may further continue in the population screening programme. However, it is necessary to also consider their age, family history, degree of bowel preparation and the quality of colonoscopy examinations.

Intermediate risk group: Patients with three or four small polyps, or one adenomatous polyp measuring ≥ 10 mm and < 20 mm, or a polyp with villous structure or high grade dysplasia, are considered to be in an intermediate risk group and should have a follow up colonoscopy in a three year interval. If there is a negative finding during the first surveillance colonoscopy another examination is indicated 5 years after the previous one. After two surveillance colonoscopies with a physiological finding, the patient can transfer to the common population colorectal cancer screening programme. If low or intermediate risk adenomas are detected, the patient should further be placed in an intermediate risk group (next surveillance colonoscopy being in a 3 year interval), in high risk polyps the next colonoscopy is recommended within 1 year.

High risk group: Patients with five small polyps or one polyp measuring at least 20mm or more are indicated to have a surveillance colonoscopy within one year from their baseline colonoscopy. If there is a negative finding or an adenoma with intermediate risk is detected, the next examination is recommended after three years. Two negative controls shift the interval for another colonoscopy by further 5 years. When a high risk adenoma is detected during a surveillance colonoscopy, an early examination is necessary – within 1 year. The aim of an early surveillance examination is to detect concurrent lesions that were not picked up during a baseline colonoscopy.

5.4 Recommendations for surveillance in chosen colonoscopy findings

Endoscopically removed pT1 carcinoma is considered a high risk lesion based on its biological characteristics, the first surveillance colonoscopy interval thus being within 12 months from the first one (Chu et al., 2003; Di Gregorio et al., 2005; Rex et al., 2006).

For surveillance purposes, serrated adenomas (i.e., traditional serrated adenomas and mixed polyps with at least one adenomatous component) should be dealt with using standard recommendations like any other adenoma. Currently, there is no data available that would explicitly certify the need for any other surveillance programme.

There has been no proof that a small hyperplastic polyp has an increased risk of colorectal carcinoma, patients with this finding are therefore placed in standard population screening programme. Individuals with one or more hyperplastic polyps measuring more than 10mm, or with non-neoplastic serrated lesions of the colon, or with multiple small lesions in the right colon, are considered to have a higher risk of developing colorectal neoplasia. However, accurate recommendations cannot be reliably determined for the current lack of data (Atkin et al., 2010).

Large sessile lesion removed by a piece-meal resection should be checked within 2-3 months, so that small areas of residual tissue can be treated endoscopically early enough. Within the next 3 months they can easily be identified using India ink tattooing and ideally completely eradicated. When a large residual finding is detected during a follow up examination, further endoscopic or surgical treatment should be considered.

5.5 Stopping surveillance

Stopping surveillance depends on several factors, not only on the characteristics of detected polyps, but also on age, comorbidities and personal wishes. The upper age boundary for surveillance colonoscopy is considered to be 75 years or older (Atkin et al., 2010). At this stage, patients can discontinue the surveillance programme and return to the population

screening programme. On the other hand, patients undergoing the surveillance programme being followed up endoscopically are not indicated to continue with the FOBT.

6. Conclusion

Colonoscopy plays a major role in colorectal cancer screening. Recently published Europeans guidelines showed that although no randomized control study on the efficacy of colonoscopy has been completed yet, the recent case-control studies found a significant reduction of 31% CRC mortality. Very promising is the NordICC trial which could confirm these results. To reduce the appearance of interval cancer, colonoscopy quality control and adequate bowel preparation is necessary. Colonoscopy can be considered an effective and safe procedure.

A well organized surveillance programme for patients with adenoma, advanced adenoma or carcinoma is just as important as a baseline colonoscopy examination with its quality and precision being the determining factors of the follow up intervals. Patients should be divided into three categories using simple criteria, depending on the presumed risk of developing colorectal cancer, while being endoscopically followed up at given intervals. It is always necessary to take into consideration age, comorbidities, personal and family history, and the personal wish of each individual.

7. Acknowledgment

8. References

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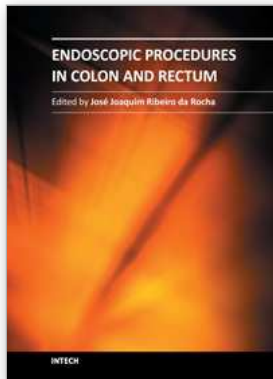
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