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Effectiveness and efficiency of CT-colonography compared to conventional colonoscopy for the early detection and diagnosis of colorectal cancer

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Health political background

Colorectal cancer (CC) is the second most common cancer and cause of cancer death for both men and women in Germany. According to the guidelines of the Federal Committee of Physicians and Sickness Funds for the early detection of cancer (Bundesausschuss der Ärzte und Krankenkassen zur Früherkennung von Krebserkrankungen) patients 55 years and older are entitled to two conventional coloscopies in an interval of ten years. The conventional coloscopy is an endoscopic examination of the colon; before the procedure, the colon must be emptied completely. Conventional coloscopy is the gold standard in the diagnosis of CC at this time.
Computer-tomography-coloscopy (CTC) is a computerised, diagnostic X-ray procedure which also requires colon preparation. The data which are provided as CT-slices are converted into a 3-D-image (virtual colography). At this time, the health insurance funds do not reimburse the costs for CTC.

Scientific background

Genetic as well as life-style factors (e. g. overweight, lack of exercise, low-fibre nutrition, alcohol abuse) are involved in the etiological and pathogenetical development of CC. It usually develops from adenomatous polyps, the risk for malignancy depending on the histological type. With increasing size and number of polyps the risk for CC rises. The importance of flat lesions and the development of CC without precursors or intermediate stages (de-novo-carcinogenesis) is being discussed.
Due to the high incidence of CC, the fact that physical discomfort often only occurs at a late stage of the disease, and the high mortality in advanced stages of CC, preventive measures in line with screening programs are taken. Through timely detection and removal of polyps, the incidence and mortality of CC can be lowered within the scope of secondary prevention. For early detection the test for occult blood in stool (faecal occult blood test) and endoscopic procedures are recommended. Due to its high sensitivity and specificity for discovering adenomas and CC, conventional coloscopy is considered the gold standard. Furthermore, it offers the advantage that in addition to extended diagnostic measures (biopsy) therapeutic measures can be taken immediately during the procedure.
In case of suspect findings during a CTC, an additional conventional coloscopy has to be undertaken (preferably subsequent to the CTC in order to avoid another colon preparation) in order to do a biopsy or polypectomy, as CTC is a purely diagnostic procedure. On the other hand, CTC allows for the concomitant depiction of other abdominal organs. An essential advantage of the CTC is the lower risk for complications through perforation and the lack of side effects or risks of sedatives, which are frequently administered before and/or during conventional coloscopy. However, radiation exposure during CTC has to be considered.

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Research questions

This report aims to answer the following research questions:

- How effective is CTC compared to conventional coloscopy for early detection and diagnosis of CC and/or precursors (polyps, adenomas)?
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- What are the ethical and legal aspects that have to be considered?

Methods

This HTA-report was prepared by applying the methods for a systematic literature review. The systematic literature search (DIMDI-HTA-superbase as well as HTA- and Cochrane-databases) yielded 1,713 abstracts. Following a two-part selection process according to standard, predefined criteria 31 medical and five economic publications were included in the assessment. 35 publications were added by hand search. A total of 201 publications was used as background literature (including publications covering ethical and legal aspects), 147 publications were excluded. Relevant texts of law regarding legal aspects were also used. Information extraction and assessment of the selected studies were performed according to predefined criteria.

Results

A total of 25 primary studies and six metaanalyses or systematic reviews are used to answer the research questions. Partly promising results for CTC regarding diagnosis are reported from individual centres comparing CTC and conventional coloscopy; however, some of these studies have a relatively small sample size and limited significance. Two multicentre studies in about 600 mostly symptomatic patients each show a sensitivity of only slightly more than 50 % for lesions of at least 10 mm.

A multicentre study in more than 1,200 asymptomatic patients with an average risk for CC shows the best results for CTC, namely approximately equal sensitivity for CTC and conventional coloscopy in the diagnosis of medium-sized and large polyps. The patient-specific sensitivity of CTC for polyps with a size of 10 mm or more is 94 % and for polyps with a size of 6 mm or more 89 %. The specificity of CTC for adenomatous polyps is 96 % for at least 10 mm diameter and 80 % for at least 6 mm diameter. In this study, four-channel and eight-channel CT scanners are used; in addition, the image quality is improved by electronic cleansing. The primary appraisal is done by highly experienced radiologists using 3-D-images. The good results are also explained by the particularly thorough colon preparation and stool tagging.

Depending on the reader, a patient-specific sensitivity between 41 and 69 % for polyps 5 to 9 mm in size and a sensitivity between 35 and 72 % for polyps of at least 10 mm is reported in a singlecentre study in more than 700 patients at slightly higher-than-average risk for CC; this shows the importance of the reader for CTC. Specificity ranges from 95 to 98 % for polyps larger than 10 mm and from 86 to 95 % for those 5 to 9 mm in size.

Some meta-analyses and systematic reviews conclude that, due to its high sensitivity and specifity CTC is generally suitable for the detection of large polyps (with a diameter of at least 10 mm). Regarding smaller lesions, the sensitivity of CTC is significantly reduced. Particularly in more recent publications, which also include a larger number of studies, the broad use of CTC in the general, diagnostic practice is not recommended because of the strong heterogeneity of results so far.

Analysing the heterogeneity, one meta-analysis shows that studies using multiple detectors report a higher and more homogenous sensitivity than those using single detectors and that a thinner collimation, as well as a combination of two-dimensional

and three-dimensional imaging yield better results. A recent systematic review cites thorough colon preparation (possibly with stool tagging), examination in supine and prone position, adequate training, and computer-supported diagnostics as additional important parameters for the optimal quality of examination.
In all systematic reviews CTC is being recommended under certain circumstances. It is essentially indicated in patients in whom a complete conventional coloscopy is not possible due to anatomical reasons or stenosing lesions. Also, CTC can yield valuable information on pathological changes proximal a tumour stenosis through identification of additional tumours or staging. Furthermore, CTC can be considered if the risk or effort of an endoscopy (or sedation) is significantly increased (e. g. in patients with blood coagulation disorders or anticoagulated patients or old and frail patients). Recent results which have not been officially published suggest that the further development of CTC in past years (towards 64-slice detectors) in combination with adequate training of the reader and corresponding evaluation modalities optimises the quality of diagnostics; thus, in the future, CTC might be considered not only for diagnostics but also for screening for CC.
All five economic model calculations refer to a screening setting. According to established screening guidelines they examine a hypothetical population of 50 year olds (at baseline) at average risk for CC who undergo a screening at certain time intervals. Three studies refer to the US, one to Canada and one to Italy. All studies evaluate the direct costs per life-year gained from the perspective of third-party payers in public health care (public health insurance or national health care service). The model calculations are of good quality, however, transparency of documentation is not always adequate.
The results show that both conventional coloscopy and CTC can be classified as cost-effective screening methods. Costs incurred by third-party payers of the health care system range from 8,090 to 18,800 USD per life-year gained for conventional coloscopy and from 8,150 to 33,800 USD per life-year gained for CTC. Compared to a scenario with no screening, one study suggests that costs can even be saved with both techniques. However, these results can also lead to the conclusion that conventional coloscopy is preferable to CTC from an economical point of view: if the procedures are compared, conventional coloscopy results in more life-years gained almost without exception. At the same time, it costs less than CTC under most scenarios.
In all studies, costs of examination and compliance are important parameters in sensitivity analysis. The sensitivity of CTC for polyps larger than or equal to 10 mm, the time interval for CTC-screening, the risk of CC due to missed polyps and the risk of complications also are of some importance. Only one study undertakes a probabilistic sensitivity analysis (in which all uncertain baseline parameters were assumed to be statistically distributed in the simulation): the probability that a CTC-screening with three-dimensional imaging in all patients and a screening interval of five years costs 100,000 USD per additional life-year gained is 38 % when uncertainty of parameters is considered simultaneously. The probability that the costs are 40,000 USD is 14 %.
Extracolonic findings during CTC and health effects and costs resulting therefrom are disregarded in the model calculations. Moreover, there is a lack of consistent consideration of a possible reduction in life quality (not only through the short-term burden during the examination, but also because of complications, extracolonic findings, or for patients with cancer). No conclusion can be drawn on how the results would be different if these things were considered.
The studies only consider the screening situation (all patients older than 50 years of age, at an average risk for CC). This is probably due to the fact that the probability of CTC being cost-effective decreases with an increasing risk for CC in the screened patient – as with an increased risk for CC, the probability increases that the patient is referred to conventional coloscopy and possibly polypectomy any-

way. The literature search for the present report yielded no economic evaluations dealing with the question if patients, in whom a conventional coloscopy is not indicated or in whom only an incomplete coloscopy is possible, should undergo a CTC for clarification.
The economic results of the five analyses conducted in the US, Canada and Italy are not directly applicable to Germany due to their different health care systems and cost structures.
In a recent German model calculation for CC-screening using conventional coloscopy, the costs for conventional coloscopy are estimated to be 197 Euro, for coloscopy including histology 209 Euro and for coloscopy with polypectomy 245 Euro. The costs of a CTC-examination in Germany can only be estimated according to the physician fee schedule for private physician services. Similar to the five model calculations its costs may be lower than the above mentioned costs for the (diagnostic) coloscopy. However, the model calculations show that only a significant difference in costs (at least about 25 % lower costs of CTC compared to diagnostic coloscopy) could possibly result in CTC being the more cost-effective procedure. In the five model calculations, compliance is assumed to range from 60 to 100 %. For Germany, this assumption seems to be too optimistic. The cumulative participation rate for screening coloscopy was 10.2 for women and 8.8 % for men from 2003 to 2005. A lower compliance at the first screening and comparably high compliance at follow-up coloscopies could favour the cost-effectiveness of CTC, as shown by one of the model calculations. Regarding compliance at follow-up coloscopy, the option to undergo this examination on the same day without additional preparation may play an important role.
Although conventional coloscopy is part of the early cancer detection program in Germany, only a relatively low percentage of the population uses this option. Even if medically indicated, CTC is not being reimbursed. Regarding the preferences of patients for one of the procedures, different studies report conflicting results. However, colon preparation, which at this time is necessary for both procedures and the painfulness of examinations are clearly important factors. Adequate patient information regarding risks and benefits of the procedures therefore is of utmost importance.
For conventional coloscopy, an agreement on quality assurance exists which lists clear standards for conducting this examination. The development of similar guidelines is called for in order to ensure quality assurance for CTC.

Discussion

Endoscopic procedures have a high reliability for diagnosing gastroenterological disorders. In addition, they have the advantage that extended diagnostic and therapeutic measures are possible during one examination, which has to be considered when comparing the efficiency and effectiveness of CTC and conventional coloscopy. The results regarding the effectivity of CTC in diagnostics and screening for colorectal cancer and/or its precursors (polyps, adenomas) are partly promising, however, they are very heterogenous for various reasons. Regarding its sensitivity and specificity, CTC cannot be considered an equivalent alternative to conventional coloscopy for diagnosis and screening. The studies, however, also show that clinically relevant polyps can be overlooked during conventional coloscopy. CTC is indicated under certain circumstances.
The higher the probability of a positive finding in CTC, the more likely it is that a referral to conventional coloscopy will be necessary; therefore, particularly patients showing high-risk symptoms or at significantly increased risk for polyps or CC may generally benefit from conventional coloscopy due to the option of immediate therapy. Economic results regarding a comparison of the

procedures in a diagnostic setting are not available. In case of incomplete coloscopies or contraindications, clarification through CTC as an alternative to contrast barium enema can be considered, as CTC has a higher sensitivity and specificity than contrast barium enema.
Before a general recommendation for CTC as a screening method for detection of CC can be made, the reasons for heterogeneity in sensitivity in the existing studies need to be clarified and consistency in data is to be demanded.
Regarding the cost-effectiveness of CTC-screening in comparison to coloscopy-screening different results are available internationally from various model calculations. On the basis of these calculations, CTC screening can be considered cost-effective compared to the option 'no screening', but – in most scenarios – not when compared to conventional colsocopy screening. The results are not directly applicable to Germany due to differences in health care systems and cost structures. Examination costs and compliance of the patients (screening compliance as well as compliance regarding a follow-up coloscopy) play an important role.
Unlike for conventional coloscopy, no established recommendations exist regarding the frequency and time interval for CTC-screening. Which approach should be taken in case of finding small polyps during CTC is also not consistently regulated. From an economical point of view, a CTC-screening every five years is more cost-effective than one every ten years; however, the increased radiation exposure and indirect costs (patient time) has not been considered.
Within the economic model calculations it is mostly assumed that any finding of polyps during a CTC leads to a coloscopy, independent of the characteristics of the polyp. On the basis of the available results no conclusion can be drawn if the cost-effectiveness of CTC will be positively influenced if only polyps of a certain size are followed up by coloscopy. In addition, it should be considered that according to some authors further CTC control examinations should be conducted in shorter time intervals if polyps are not removed. This approach requires a high compliance of the patient and also causes additional radiation exposure. Furthermore, no data currently exist on the development of small polyps and the relevance of flat lesions.
In contrast to coloscopy, extracolonic diagnoses can be discovered as chance findings – some with clinical relevance – during CTC. From an economical point of view, extracolonic findings lead to an increase of diagnosis- (and treatment-) costs; however, they can also cause cost-savings by preventing sequalae. They have not been considered in the available analyses.
Particularly when screening healthy persons, the risk of the examination is of importance. In general, CTC is assumed to have a lower risk profile than conventional coloscopy. Of relevance for CTC are radiation exposure and a minimal risk of perforation.
An important ethical aspect is the consideration of patient preferences regarding the procedures, as especially in the context of screening both procedures are demanding and perceived to be unpleasant. Technical improvements of CTC which make a less demanding colon preparation possible could increase compliance for screening examinations. Furthermore, adequate patient information regarding benefits and risks are of importance. The fact that even when medically indicated CTC is not being reimbursed in Germany has to be taken into account as a social aspect. Apart from patient information and education, legal aspects especially pertain to stipulation and adherence to quality standards.

Conclusions/recommendations

At this time, a clear endorsement of CTC as an alternative procedure for conventional coloscopy which is agreed to be the current gold standard cannot be given either for diagnosis or for screening. On the basis of the available literature this holds true for both the medical as well as the economic assessment. However, despite the numerous studies and analyses on this topic, this assessment is afflicted with uncertainties (large heterogeneity of medical results, no model calculation for Germany).

Indications for diagnosing CC using CTC exist. If modern CTC-devices are used with adequate technical setting, software, and adequate training of the reader, better results regarding sensitivity can be expected according to recent studies. To what extent these results can be utilised in clinical everyday practice has to be examined depending on the technical equipment and training. Similarly to the agreement on quality assurance standards for coloscopy in Germany, the development of similar guidelines is recommended for CTC.

The rapid technological development of CTC during the past years and newly published study results require short-term revisions regarding these research questions.

In order to recommend CTC for screening, studies aiming to determine an appropriate screening interval while taking into account radiation exposure, and regulation of the approach to be taken when finding polyps are desirable. Regarding the relevance of flat or depressed lesions further research is necessary. In studies comparing CTC and conventional coloscopy, adequate sample sizes should be aimed for; also, complete presentation of data in the publications (e. g. technical aspects including radiation dose, software, assessment modalities, training and experience of the readers for both procedures) is essential to make results transparent and comparable.

In order to appraise the cost-effectiveness of a CTC-screening in Germany, a model calculation adjusted to the German situation is necessary (possibly by adapting existing model calculations). However, the results of ongoing studies on the sensitivity and specificity of CTC should be awaited.