HAS
HAUTE AUTORITÉ DE SANTÉ

VIRTUAL COLONOSCOPY
META-ANALYSIS OF DIAGNOSTIC ACCURACY
INDICATIONS AND CONDITIONS OF USE

SHORT TEXT of the technological evaluation report

January 2010

Diagnostic and therapeutic procedures assessment department

This report was validated by the HAS Board in **January 2010.**

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INTRODUCTION

Checking for cancerous or precancerous lesions is one of the main indications of colorectal investigation. The incidence and mortality of colorectal cancer make it a major public health problem in industrialised countries. Colorectal investigation is either a diagnostic procedure, done on account of various suggestive symptoms, or a preventive measure if the aim is early screening for any cancerous or precancerous lesions.

Video colonoscopy is currently the reference standard for examination of the colorectal mucosa. It does however require systematic preparation of the colon and in most cases sedation. Occasionally, video colonoscopy does not allow complete investigation of the colon. In rare instances it is associated with undesirable effects which can nevertheless prove to be potentially severe (haemorrhage, perforation). These constraints, limits and even risks then prompted the development of alternative means of colonic investigation (colonic CT, virtual colonoscopy, colonic capsule endoscopy).

Among these alternatives, virtual colonoscopy is currently presented as the most successful. Virtual colonoscopy, a computed tomographic examination technique developed 15 years ago, has been the subject of contradictory publications, with initial favourable study in 2003 followed by a more questioning attitude in 2004-2005 when publications failed to reproduce the same level of diagnostic performance. Finally, the publication in 2008 of a multicentre study which recruited more than 2500 patients and presented favourable results once again made virtual colonoscopy the focus of medical debate on colonic investigation.

In this context, in the first half of 2008 HAS was asked, by the French Society of Radiology (SFR) and the Federation of Specialists in Gastrointestinal Diseases (FSMAD), to update its assessment of virtual colonoscopy. This request followed 2 earlier assessments of virtual colonoscopy by the National Health Accreditation and Assessment Agency (ANAES): one in 2001 ("The place of virtual colonoscopy in the investigation of colorectal cancer"), the other in 2004 ("Endoscopy of the lower digestive tract: indications outside population screening", professional recommendations). Whereas in 2001 virtual colonoscopy was regarded as an emerging technique, the 2004 assessment recognised the possibility of using this examination in cases of incomplete colonoscopy (grade C). Virtual colonoscopy is not currently included in the Common Classification of Medical Procedures (CCAM).

The aim of this report is to assess the diagnostic performance of virtual colonoscopy and to identify the main factors guaranteeing optimum results (definition of conditions of use). The diagnostic performance and safety of virtual colonoscopy will be compared directly with those of video colonoscopy. This assessment of the risk-benefit ratio will then be used to specify the indications for this examination.

The assessment of virtual colonoscopy is linked to 2 main issues. The definition of new indications for virtual colonoscopy could produce a significant change in the strategies for diagnosis and screening for colorectal polyps and cancers (public health interest). This change could then have an impact on the field of activity of gastroenterologists and radiologists (medical practice interest).

MEDICAL CONTEXT OF THE ASSESSMENT

## I. GENERAL PRESENTATION OF VIRTUAL COLONOSCOPY

Virtual colonoscopy (VC) is a computed tomographic method of investigating the colon that has been described and developed since 1994. This examination is carried out in 4 successive stages: preparation of the colon, distension of the colon with a gas (insufflation of air or CO_2), acquisition and reconstruction of the computed tomographic data and finally reading the images using dedicated software. In particular, reading the VC examination involves a three-dimensional reconstruction of the colon which simulates the images obtained by video colonoscopy. This reading method gave rise to the current term "virtual colonoscopy".
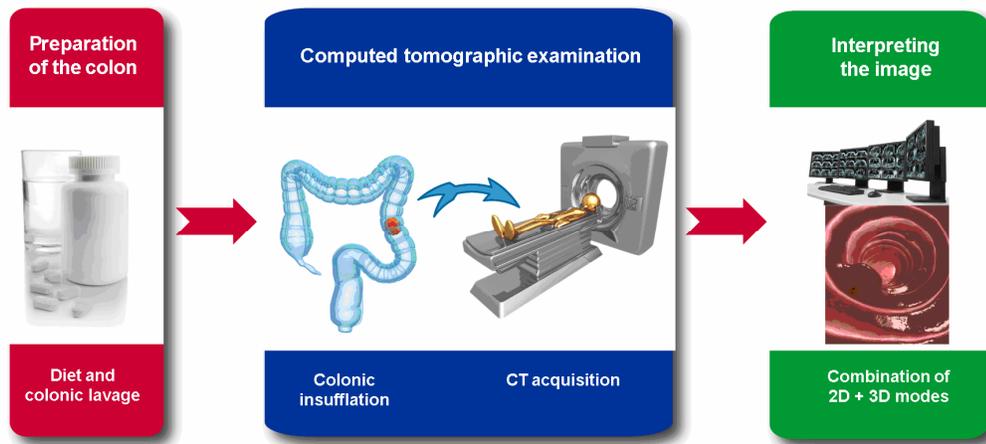
The use of a gas as contrast medium distinguishes VC from water-based colonic CT. Almost all the published clinical studies are devoted to VC's ability to detect cancerous and precancerous colorectal lesions (i.e. colorectal cancers and polyps).

II. COLORECTAL CANCER AND POLYPS

Colorectal cancer is the 3rd commonest cancer in France (about 37,000 incident cases in 2005) and the 2nd commonest cause of death from cancer (16,800 deaths in 2005). This cancer affects mainly those over 50 years of age (94% of the cases observed). It is estimated that 60-80% of colorectal cancers arise from an initially benign epithelial lesion called an **adenomatous polyp** or a **colorectal adenoma**. This lesion poses a risk of malignant transformation after a long period of development ("**adenoma-cancer sequence**").
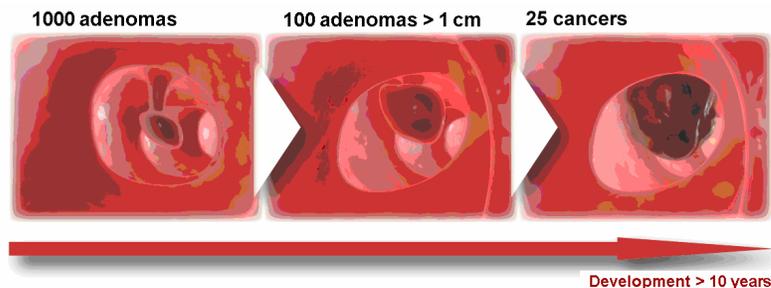
The adenoma-cancer sequence warrants making the excision of this particular histological entity a priority. **Video colonoscopy** and **radiological investigations do not however make it possible to predict the** possibly **risky nature of a** visualised colorectal **lesion**. Consequently, the aim of these examinations is more

broadly to identify the presence of any colorectal polyp or mass. Defining a lesion's histological type is still the prerogative of pathological examination alone. This result will then determine the immediate treatment approach to be adopted and the monitoring offered to the patient (2004 ANAES recommendations).

Colorectal polyps are a heterogeneous group of lesions which are customarily differentiated in the literature and in practice on the basis of their morphological appearance (pediculate, sessile and flat), size and histological type. **Small polyps** (≤ 5 mm) and **flat lesions** are not assessed uniformly within the medical community. They are currently giving rise to numerous debates about their prevalence, their importance as precursors of colorectal cancer and what to do about them if they are identified during colonic investigation.

III.   A CANCER THAT CAN BE DETECTED IN TWO SETTINGS

The initial stage in the development of colorectal cancer is silent, which is why only a minority of these lesions are detected in the first stage of their development (the stage associated with the highest relative survival rate). These factors thus justify the use of **screening techniques**.

On the other hand, certain signs can be suggestive of CRC and thus prompt **diagnostic investigation of the colon** (alteration in intestinal transit, gastrointestinal bleeding, etc.). These signs are not specific to a colon complaint or predictive of the neoplastic nature of any colon disorder. This lack of specificity thus means using an examination that is capable of diagnosing and differentiating between these various potentially underlying colon disorders.

Three levels of colorectal cancer risk are defined. Thus, a distinction is made between individuals at **moderate risk** of colorectal cancer (almost 80% of the general population), those said to be at **high risk** (15-20% of the general population) and finally those at **very high risk** (1-3% of the general population).

Medium risk	High risk	Very high risk
• Asymptomatic individual aged 50-74 years	• Personal history of adenoma or CRC • History of CRC in first-degree relative • Pancolitis developing for more than 10 years	• Member of a family with familial adenomatous polyposis (FAP) • Member of a family affected by hereditary non-polyposis colorectal cancer (HNPCC)

CRC: colorectal cancer

In France, organised general screening has been established. It is aimed at subjects at medium risk who are 50 to 74 years of age (16 million individuals) and is based on video colonoscopy being carried out where the faecal test for occult blood is positive (positive results seen in 2-3% of cases). The screening applied to patients at high or very high risk is based mainly on video colonoscopy the frequency of which varies according to the patient's medical history and the results of any earlier colonic investigations.

IV. CURRENT PLACE OF VIRTUAL COLONOSCOPY IN COLONIC INVESTIGATION PRACTICE

In 2001, ANAES felt that the data available did not allow it to recommend the use of VC in screening for colorectal cancer (a procedure considered to be still at the development stage). In 2004, ANAES included VC in the list of non-endoscopic morphological examinations recommended in cases of **incomplete video colonoscopy**. It is thus the only validated indication for VC at the time of this report.

PURPOSE AND METHOD OF ASSESSMENT

The method of assessment used in this report is based on a critical analysis of data from the scientific literature and the reasoned position of healthcare professionals in a working group (14 representatives of the French Society of Radiology (n = 5), the Federation of Specialists in Gastrointestinal Diseases (n = 4), the French Federation of Gastrointestinal Oncology (n = 1), the French Society for Pathology (n = 1), the Federation of Gastrointestinal Surgery (n = 1), the National Cancer Institute (INCa) (n = 1) and the Health Monitoring Institute (INVS) (n = 1)).

This report assessed the level of standardisation in VC, the diagnostic accuracy of this examination and the safety and tolerability of its use. This approach allowed the indications, contraindications and conditions for use of this procedure to be defined.

The influence of VC on colorectal cancer mortality has not been defined. Failing that, the diagnostic accuracy of this procedure was defined by assessing its ability to identify colorectal cancers and polyps (main area of assessment). The **meta-analysis method** had to be used in order to assess and take account of the substantial inter-study heterogeneity associated with this criterion.

A **systematic descriptive review method** supplemented the meta-analysis. It allowed an analysis to be made of the factors determining the diagnostic performance of VC, its safety, tolerability and the particular diagnostic contribution made by this examination (extra-colonic discoveries, ability to detect flat lesions, computer aided diagnosis software). Standardised and computerised data extraction was used for each of these fields, with a specific database created each time. This data extraction was carried out independently of the diagnostic performance results for VC.

The **literature search carried out**, covering the period **2001-2009**, identified **1294 publications**.

META-ANALYSIS OF DIAGNOSTIC PERFORMANCE

The meta-analysis strategy and statistical methods used were defined before any data on the diagnostic efficacy of VC were extracted. A meta-analysis protocol recording these choices was prepared.

I.   BIBLIOGRAPHIC SELECTION STRATEGY

Of the publications identified, 108 studies presented results directly comparing the diagnostic performance of VC with that of video colonoscopy (studies identified in a double selection procedure). **24 comparative studies** that included **7202 patients** were **retained** after redundant publications had been discarded and the inclusion and exclusion criteria had been applied (publications were independently selected by 2 reviewers with any discrepancy in judgement resolved by consensus). Only studies fulfilling the following selection criteria were included:

– prospective studies that enrolled adult patients undergoing CTC after bowel preparation and having secondary OC as the reference exam, with CTC and OC interpreted in a blinded fashion (at least a first blinded OC in case of tandem OC);

– studies that reported the use of a multidetector CT scanner with systematic dual acquisitions and with slice collimation no greater than 2.5 mm;

– studies that described polyp-matching procedure used to address uncertainties in comparative localization, size or morphology between CTC and OC;

– studies that presented results of CTC read without the help of computer-aided diagnosis system.

Studies reporting more than 15% of incomplete OC or reporting CTC procedures without prior colonic preparation were excluded.

These selection criteria served to guarantee that these studies conformed to current French practice and met the technical standards defined by international expert consensus (multislice acquisition with 2 angles of incidence and a mean nominal thickness of ≤ 2.5 mm). None of the 5 meta-analyses published at the time of this report satisfied this requirement.

II.   METHODS OF DEFINING DIAGNOSTIC PERFORMANCE

Rating the diagnostic performance of VC involves making a **triple assessment** of an experimental unit (*"per lesion"* or *"per patient"*), and of the size and histological type of the lesions in question.

The *"per lesion"* unit describes VC's ability to detect **each target colonic lesion** belonging to a predefined size category. The "per patient" unit describes VC's ability to detect **at least one lesion among those** present **in the size category under consideration**. Only the "per patient" unit can be used as a basis for rating the specificity of VC investigation (ability to count "true negative" patients, as opposed to those with "no lesions").

The meta-analysis in this report was made using summary data from the 24 comparative studies included. For each one, priority was given to the diagnostic performance of VC expressed without any histological restriction ("per polyp" result; if unavailable, data restricted to adenomatous lesions were extracted). To this end,

raw data were **extracted** by a **standardised method** using a **specific grid** by **2 evaluators, initially separately from** one another.

III. STATISTICAL METHODS

The heterogeneity of the combination of results from the studies selected was **evaluated statistically** (χ^2 test and its resulting I² test). Where there was excessive heterogeneity (I² > 50%), the sensitivities and specificities of the studies were combined using a **mixed model** (Markov chain Monte Carlo method). If this was not the case, a fixed effect model was to be used (with each study result weighted for the corresponding patient or lesion population).

The diagnostic performance of VC was compared directly with that of video colonoscopy ("per patient" unit, χ^2 test).

The influence of 4 covariables on the diagnostic performance of VC was studied by means of subgroup analyses defined *a priori*. These 4 covariables corresponded to the type of colonic preparation (optimal *vs.* standard), the **nominal slice thickness** (($\leq$ 1 mm) *vs.* (1-2.5 mm)), the **charge applied** during **acquisition** ((50-70 mAs) *vs.* ($\geq$ 100 mAs)) and the primary **reading mode** (2D *vs.* 3D).

IV. RESULTS OF THE META-ANALYSIS

All the results given in this meta-analysis were obtained using a **mixed model**, on account of **constant excessive heterogeneity**. The global performance of VC was thus associated with **broad confidence intervals** (intervals with a range of 12-17% for "per patient" sensitivities and a range of 3-39% for "per patient" specificities). Variable VC performance can thus be assessed objectively in practice.

This meta-analysis rates the **"per lesion" sensitivities** of VC at:

– **0.31** (95% CI: 0.22-0.40) for "lesions of **≤ 5 mm**";

– **0.67** (95% CI: 0.60-0.74) for "lesions of **6-9 mm**";

– **0.81** (95% CI: 0.76-0.87) for "lesions of **≥ 10 mm**".

This meta-analysis thus rates the *"per patient"* sensitivities and specificities of VC as follows:

	"Per patient" sensitivity		"Per patient" specificity	
	Global index	95% CI	**Global index**	95% CI
"Lesions ≥ 1 mm"	**0.68**	0.59-0.76	**0.58**	0.38-0.77
"Lesions ≥ 6 mm"	**0.80**	0.74-0.86	**0.86**	0.80-0.91
"Lesions ≥ 10 mm"	**0.84**	0.77-0.90	**0.97**	0.95-0.98

The *"per patient"* **sensitivities** of **VC** are **significantly lower** than those of **video colonoscopy**. By comparison, this meta-analysis evaluates the *"per patient"* **sensitivities** of video colonoscopy at **0.94** (95% CI: 0.91-0.96) for "lesions **≥ 1 mm**", **0.94** (95% CI: 0.92-0.96) for "lesions **≥ 6 mm**" and **0.93** (95% CI: 0.89-0.96) for "lesions **≥ 10 mm**".

The sensitivity/specificity pairings for VC that were defined thus make this examination of great diagnostic interest for lesions of more than 10 mm, moderate diagnostic interest for lesions of more than 6 mm and of low diagnostic interest for those of any other size.

The **subgroup analyses** identified **three covariables** that have a **significant interaction** with the **diagnostic performance** of VC. These are the tagging of faecal residues (sensitivity gain of 14-17%), a nominal slice thickness of not more than 1 mm (gain of 4-19%) and a 3D primary reading mode (sensitivity gain of 10-13% for the detection of lesions of less than 10 mm).

The method and results of the meta-analysis were validated unanimously by the working group.

SPECIAL DIAGNOSTIC CONTRIBUTIONS OF VIRTUAL COLONOSCOPY

I. VIRTUAL COLONOSCOPY IN A SETTING OF INCOMPLETE VIDEO COLONOSCOPY

In France, about 5% of video colonoscopy procedures every year do not reach the fundus of the caecum and are therefore classed as incomplete (50,000-60,000 incomplete procedures/year). This incomplete status is due to an obstructive colorectal lesion (*e.g.* obstructive cancer) or a nonobstructive cause (*e.g.* poor colonic preparation (30-40% of incomplete video colonoscopies), technical difficulty linked to colonic loops or angulations).

The loss of opportunity associated with this incomplete status may promote the use of an additional colonic investigation. VC and water-based colonic CT are 2 of the main alternatives to video colonoscopy in this indication.

This setting for the use of VC has been the subject of only a limited number of published material (systematic review, 9 studies, 1230 patients). The VC procedure was technically feasible in 86-100% of those cases. These published data were nevertheless too fragmentary for a description of the diagnostic performance, safety and tolerability of VC in this setting.

The members of the working group decided that the literature data did not permit the definition of the respective places of VC and the alternatives to incomplete video colonoscopy mentioned by the 2004 ANAES evaluation. They thought that "*Virtual colonoscopy can be offered after incomplete video colonoscopy*" (strong agreement, median: 9).

II. EXTRA-COLONIC FINDINGS IN VIRTUAL COLONOSCOPY

Extra-colonic findings (ECF) in VC were defined as occult extra-colonic abnormalities with a potential impact on the clinical management of the patient involved. This definition is the closest reflection of the contribution made by VC in this situation.

The systematic descriptive review of this field of evaluation involved the analysis of 17 studies (9591 patients). In these studies, VC allowed the identification of an extra-colonic lesion in 5-34% of examinations, with 1.7% of patients showing extra-colonic cancer (affecting mainly the liver and kidneys).

The working group felt that: "*The literature does not allow an assessment to be made of the influence of ECFs on patient management*" (relative agreement, median: 9). Several members of the working group pointed out that these ECDs were associated with a risk/benefit ratio which could not be formally agreed by consensus due to the lack of adequate literature data. The working group stressed that VC could not in practice be compared to an abdominal scan for the diagnosis of extra-colonic abnormalities, since the main purpose of VC was colonic investigation.

III. ABILITY TO DETECT FLAT COLORECTAL LESIONS

There are only preliminary data on the definition of VC's ability to detect flat lesions (systematic review, 6 studies, 141 flat lesions recorded). The definition of these lesions differs between the VC technique and that of video colonoscopy. The sensitivity with which these flat lesions are detected by VC seems to be variable (sensitivity "per flat lesion ≥ 6 mm in diameter": 0.2-0.8). It is systematically less than that of video colonoscopy. This analysis was validated by the working group (strong agreement, median: 9).

IV. COMPUTER AIDED DIAGNOSIS SOFTWARES

Computer Aided Diagnosis (CAD) softwares consist of a computer algorithm which must be capable of identifying and locating, without human intervention, the presence of any colorectal polyp or cancer. CAD softwares were developed to increase the accuracy of reading VC examinations, reduce the impact of inter-reader variability and reduce the examination reading time.

Only a limited number of publications define the diagnostic impact of combining CAD software with "human" reading (5 studies; 459 VC examinations recorded). At present, there seems to be an objective diagnostic benefit only in inexperienced readers (increase in reading sensitivity of 10-20%, with a more or less identical reduction in reading specificity). The qualifier "inexperienced" applied to the human reader is however not defined precisely in the literature.

The members of the working group thought that CAD software could usefully supplement "human" reading but without replacing either the need to train the inexperienced reader or this "human" reading.

SAFETY AND TOLERABILITY OF VIRTUAL COLONOSCOPY

I. SAFETY OF THE PROCEDURE

The safety of the VC procedure was evaluated in a systematic descriptive review of the early complications associated with this examination (mainly colonic perforation) and the risks linked to exposing patients to ionising radiation. For comparison purposes, video colonoscopy is associated, in its diagnostic phase, with complications mainly involving a perforation rate of 0.1 to 1‰. These complications are fatal only in exceptional cases.

I.1 Systematic review of direct comparison studies (VC vs. video colonoscopy)

None of the 22 studies selected (48,455 patients) reported any fatal complications associated with VC or video colonoscopy. Two serious complications were associated with VC (1 hospital admission on account of severe vomiting, abdominal pain, 1 case of bacteraemia), 6 with video colonoscopy (1 perforation, 4 haemorrhages, 1 bacteraemia). The rarity of these events made a statistical comparison completely impossible.

I.2 Systematic review of observational studies

The 8 observational studies analysed (62,373 patients) yielded only 24 complications, none of which were fatal (overall frequency: 0.5‰). Colonic perforation was the main serious complication (0-0.6‰). A third of these perforations (mean) were treated surgically; this figure was subject to great variability (11-57%).

The working group thus thought that serious complications of VC were rare and involved mainly colonic perforation (relative agreement, median: 7). The members of the working group believed that the safety of VC was mainly determined by the colonic insufflation techniques. For this reason, performing automated insufflation of CO_2 was presented by the working group as a mean of reducing the risks of colonic perforation. The working group thus thought that the observational studies overestimated the risk of complications with VC because in these studies insufflation was in most cases performed manually with room air.

I.3 Risk linked to exposing patients to ionising radiation

The assessment of patients' exposure to ionising radiation was limited by the variability of the effective doses that were associated with VC and presented in the literature. The long-term cancer risk associated with this irradiation proved very difficult to quantify: it is not measurable, since insufficient time has passed and its evaluation is based on controversial models. The working group confirmed this evaluation result and thought that "*According to the literature data, VC performed without the injection of contrast medium is associated with weak irradiation which is generally less than that of an abdominal scan*" (strong agreement, median: 8).

II. PROCEDURE ACCEPTABILITY

The literature analysed does not propose any single measure of patient acceptability of the VC procedure. Because of that, data on tolerability and patient preference were evaluated in this report as factors predictive of acceptability. A systematic

review of 20 studies (5554 patients) comparing the gastrointestinal and emotional tolerability of VC with that of video colonoscopy produced conflicting results. Patients' preference for VC (10-92% of patients) or video colonoscopy (5-65% of patients) seems to be very varied. This analysis was moreover limited in its conclusions because of the use of a sedation practice in video colonoscopy that differs from standard French practice (85-90% of procedures are conducted under sedation in France). The working group also stressed that the way in which VC was performed in these studies was obsolete (in most cases manual insufflation of air). The working group believes that better acceptability was observed in practice with procedure involving mechanical insufflation of CO_2.

RECOMMENDATIONS ON THE USE OF VIRTUAL COLONOSCOPY

Referring to the results of the meta-analysis made by HAS but also the opinion of the working group, international expert consensus (American College of Radiology; American Gastroenterological Association; European Society of Gastrointestinal and Abdominal Radiology), the radiological procedures guide of the French Society of Radiology and the respective positions of VC and video colonoscopy defined by the professional bodies involved, HAS defined the current validated indications and contraindications for VC. These indications concern only the detection of colorectal polyps and cancers. They are given in terms of the patient's level of colorectal cancer risk so that they can be incorporated into the current practice recommendations.

I.   INDICATIONS FOR VIRTUAL COLONOSCOPY

I.1   Incomplete video colonoscopy

HAS believes that VC can be offered after incomplete video colonoscopy. In this indication, the choice of investigation method will take account of the reason for this failure of video colonoscopy, the indication for colonic investigation (type of colonic lesion being investigated) and the patient's comorbidities. At the time of this report, there are insufficient published data to give a formal ranking of the alternatives to video colonoscopy in this context.

I.2   Diagnosis of colonic symptoms

HAS believes that a patient presenting with colonic symptoms suggestive of tumour should undergo investigation by video colonoscopy. VC could be an alternative in the following cases:

-   refusal of investigation by video colonoscopy after full and fair information of the patient;
-   comorbidities, mainly cardiopulmonary, compromise the safety of video colonoscopy.

I.3   Screening of patients at medium risk of colorectal cancer

HAS believes:

-   that VC does not meet the requirements for an organised first-line screening test for patients at medium risk of colorectal cancer;
-   that video colonoscopy must be offered as a first-line investigation for patients at medium risk of colorectal cancer who have had a positive faecal test for occult blood in the stool. In this situation and in accordance with the opinion of the national group on the follow-up of organised screening, HAS believes that VC can be offered in cases where comorbidities jeopardise the safety of video colonoscopy. In this same context, HAS believes it is not possible to give a ruling on a situation where video colonoscopy is refused. This issue requires consultation of the bodies that run the colorectal cancer screening program so that a coordinated response can be given but also so that specific data from this

programme can be extracted. HAS is thus going to evaluate this question specifically and will seek information from the parties involved in this matter.

I.4 Screening of patients at high risk of colorectal cancer

HAS believes that screening a patient at high risk of colorectal cancer needs to be done using video colonoscopy. VC can be offered in the following cases:

- refusal of investigation by video colonoscopy after full and fair information of the patient;
- comorbidities, mainly cardiopulmonary, compromise the safety of video colonoscopy.

I.5 Screening of patients at very high risk of colorectal cancer

HAS believes that screening a patient at very high risk of colorectal cancer must be done exclusively with video colonoscopy.

II. CONTRAINDICATIONS TO THE USE OF VIRTUAL COLONOSCOPY

As with **any computed tomographic procedure**, pregnancy is considered an **absolute contraindication**, which means that the possibility of pregnancy must be excluded in women of child-bearing age, particularly if an effective means of contraception is not used.

The **absolute contraindications** to the insufflation procedure are cases of suspected colonic perforation, complete occlusion syndrome, diverticular sigmoiditis, acute colitis, the scar-forming phase after supracentrimetric polypectomy or endoscopic mucosectomy.

Other situations require a special assessment of the risk/benefit ratio for VC (**relative contraindications**), such as recent medical history (< 3 months) of abdominal or hernia surgery, or surgery for partial colorectal resection, chronic inflammatory intestinal diseases, proctological lesions likely to compromise the tolerability of inserting a rectal probe, anal incontinence complicating the colonic insufflation phase, mental disorders or severe respiratory insufficiency which compromises patient cooperation.

III. LIKELY PROSPECTS

The working group wished to look at the action to be taken on the discovery of polyp(s) following a VC examination. There are however 3 main stumbling blocks in this area, namely:

- the fact that there is limited agreement between the measurements made in video colonoscopy and VC;
- the lack of consensus on the need for systematic excision of colorectal lesions less than 6 mm in size (strong agreement; median: 9) ;
- a lack of factual and published data that can be used to define the follow-up of a patient with no colorectal lesions after VC.

The members of the working group thought that "the discovery of a polyp 6 mm or more in size after VC means referring the patient for excision or biopsy of this lesion" (strong agreement; median: 9).

Defining the action to be taken following the discovery of colorectal lesions less than 6 mm in size requires an independent evaluation of any colonic investigation procedure. The method and purpose of this evaluation of VC does not allow this practical issue to be resolved. At the time of this report, there is no systematic and independent evaluation of this specific subject which challenges the recommendations drafted in 2004 by ANAES ("Lower gastrointestinal endoscopy: indications outside population screening", professional recommendations). The professional organisations involved in this issue were asked to consider the need to make a specific referral to HAS. In the absence of any consensus, in 2008 the professional bodies (the French Society of Gastrointestinal Endoscopy (SFED), the French National Society of Gastroenterology (SNFGE) and the French Society of Radiology (SFR)) recommended, in a document entitled "The respective positions of colonic CT and colonoscopy", the resection of any polyp detected in VC, whatever its size.

HAS believes that the discovery of a polyp 6 mm or more in size after VC means referring the patient for excision or biopsy of this lesion. In the absence of an independent study giving a recommendation and since there is no consensus assessment, HAS cannot give a ruling on the action to be taken on the discovery, during a virtual colonoscopy examination, of a polyp less than 6 mm in size.

CONDITIONS FOR CARRYING OUT VIRTUAL COLONOSCOPY

I. PREPARATORY STAGES

Agreement between prescriber and radiologist allows the indication to be validated and colonic preparation to be adapted to any comorbidities the patient may have. The patient information, provided orally and in the form of a written document, contains clear explanations of the stages of colonic preparation, the examination procedure, the expected benefits and the potential risks of the VC technique. **Colonic preparation**, applied systematically, combines a 1-2 day residue-free diet and the oral administration of a colonic lavage product. This product contains sodium phosphate, which the working group regards as leaving few liquid residues, or polyethylene glycol (PEG). The choice between these two active ingredients is guided by the centre's usual practices, any comorbidities the patient may have and the summary of product characteristics. In the absence of any specific contraindication, tagging of the liquid and solid faecal residues is recommended since it improves diagnostic performance.

II. TECHNICAL PROCEDURE

Colonic distension, preferably performed via the automated insufflation of CO_2, is controlled by patient feedback, the volume and pressure of insufflation and by creating a bitmap before each acquisition phase. The injection of an antispasmodic treatment is optional, as is that of an intravenous contrast medium (where needed to optimise the search for extra-colonic lesions).

Two acquisitions, with breath-holding and supine (dorsal and ventral, or 2 lateral positions), should be performed using a multidetector scanner. This acquisition phase is characterised by a nominal slice thickness of not more than 2.5 mm (preferably less than 1.5 mm), a millimetric reconstruction step, a breath-holding period of max. 15 sec and a helical length permitting complete visualisation of the colonic frame. For optimal radiological protection of the patient, the recommended voltage is tailored to the patient's morphotype and is between 80 and 120 kVp, the charge less than 100 mAs. The dose*length product (DLP) is less than 500 mGy*cm for patients of normal build.

III. READING THE EXAMINATION

The VC examination is analysed by a single reader with an extensive knowledge of computed tomographic practice and physical signs. **Initial training of the reader** is necessary and is based on a minimum of 50-75 VC examinations of lesions validated beforehand by video colonoscopy and characterised by varying signs and morphologies. It includes the study of specific procedures for improving the detection of lesions (varying the density, electronic subtraction, etc.) and different reading modes.

Reading initially consists of 2D-mode interpretation of investigations for supra-centrimetric, circumferential colonic lesions or extra-colonic abnormalities. Next, an exhaustive check of lesions of any size is made which always combines a primary detection mode with a secondary confirmation mode. The reading station used must allow at least simultaneous examination of 2D and 3D views obtained from 2 additional acquisitions, continuous plotting of the reading position on the colonic frame and quick switching of the density windows in 2D mode. It is advisable to use electronic subtraction of the tagged residues. Reading support software can be used, but it cannot eliminate the need to train an inexperienced reader or to use a "human" reader. The result of this reading will appear in the examination report.

CONCLUSIONS

Six main conclusions can be drawn from the evaluation of virtual colonoscopy (VC) presented in this report:

1) Diagnostic performance rated by meta-analysis

The diagnostic performance of VC which can be defined concerns only cancerous or precancerous colorectal lesions (polyps).

The meta-analysis made by HAS is the only analysis of this type to include only studies which conform to current technical standards. VC is of great diagnostic interest in the detection of colorectal lesions larger than 10 mm, moderate interest for those larger than 6 mm and low interest for lesions of any other size (lesions ≥ 1 mm).

In the studies analysed, this performance is very mixed and poorer than that of video colonoscopy. In practice, variability in the performance of VC is to be expected because of the potential influence of multiple factors during its use (in particular methods of colonic preparation, acquisition parameters and reading modes).

2) Special diagnostic contributions of virtual colonoscopy

An occult extra-colonic lesion is discovered during 5-35% of VC examinations, although it is not possible to specify the influence this has on patient management. Consequently, and because of the specific technical features of VC, this examination cannot be compared to a standard abdominal CT scan.

There are only preliminary data on VC's ability to detect flat colorectal lesions and the results are variable and inferior to those for video colonoscopy.

No formal details can be given of the value and methods of using computer aided diagnosis software since there are insufficient data.

3) **Safety**

The literature analysed shows that severe complications of VC are rare (0-4‰) and involve mainly colonic perforation (0-0.6‰). The safety of VC seems to be linked mainly to methods of colonic insufflation. However, the published data do not allow any direct comparison to be made with the safety of video colonoscopy.

VC is described as being associated with weak irradiation of the patient. If no intravenous contrast medium is injected, this irradiation is presented as less than that of a standard abdominal CT scan.

4) Indications for virtual colonoscopy

VC is not a first-line examination for colonic investigation but is an alternative to video colonoscopy in particular situations. These indications have evolved since the previous evaluation in 2004 by ANAES.

VC can be offered in cases of incomplete video colonoscopy. In the context of diagnosing symptoms suggestive of colorectal tumour or of screening patients at high risk of colorectal cancer, VC can be offered if video colonoscopy is refused or if comorbidities compromise the safety of video colonoscopy. In this context, contraindications linked to general anaesthesia are nevertheless rare. When screening patients at medium risk of colorectal cancer, VC can be offered where

there is a medical contraindication to video colonoscopy in a patient who has tested positive for occult blood in the stool.

VC is not an examination for screening patients at very high risk of colorectal cancer.

5) Guidelines on the definition of conditions of use

The conditions of use given priority in this report which were agreed by the professionals consulted focus on obtaining optimal diagnostic performance in VC examinations. Performance is thus very close to that of video colonoscopy. These conditions of use require complete preparation of the colon (diet, colonic lavage, double tagging of faecal residues), acquisition and reconstruction techniques which promote high spatial and temporal resolution (double acquisition, thin overlapping slices) and strict reading of the examination (trained reader, combination of modes). Moreover, other conditions of use enhance the safety of VC. These are special methods of colonic insufflation (mechanical insufflation of CO_2) and limited irradiation. Finally, these conditions of use must allow the potential variation in VC performance to be limited in practice, as mentioned at the start of these conclusions.

6) Likely prospects

a) Situation regarding practice in France

The situation regarding VC practice in France must be defined, since there were no published data at the time of this report. VC is part of a Support Programme for Innovative and Costly Technologies (STIC). This study, carried out as part of STIC 2005, has aims different to those of the HAS report: its main aims are to determine the health economics impact of VC and to evaluate different methods of reading and reader training. HAS was informed that the initial results of this study would not be available before March 2010.

b) The place of VC in patients with a positive Hemoccult® test who refuse video colonoscopy

This assessment of VC will be followed by another assessment by HAS (Department of Economic and Public Health Assessment). This will make it possible to define the potential place of VC when video colonoscopy is refused by a patient at medium risk of colorectal cancer who has tested positive for occult blood in the stool. This will require additional data that are not available at the time of this assessment. This assessment will also call for coordination with the bodies involved in organising screening for colorectal cancer.

c) Action to be taken on the discovery of colorectal lesions less than 6 mm in size

At the time of this report, there is no consensus on the action to be taken on the discovery of colorectal lesions less than 6 mm in size, and this would require an independent assessment of practice in any colonic investigation procedure. The professional bodies concerned have been asked to assess the need to refer this matter to HAS.