衞生防護中心
Centre for Health Protection

Colorectal Cancer Screening Programme Task Force

Recommendations on Management of CRCSP participants who had positive FIT and negative colonoscopy findings

Background

In Hong Kong, the Government's Subsidised Colorectal Cancer Screening Programme (CRCSP) adopted a 2-tier screening workflow. Programme participants will first receive subsidised Faecal Immunochemical Test ("FIT") (a version of Faecal Occult Blood Test which is simple and does not require restriction on diet or medication) from enrolled Primary Care Doctor ("PCD"). If the FIT result is positive, the participant will receive subsidised colonoscopy examination service from enrolled Colonoscopy Specialist ("CS").

2. Among participants who had positive FIT results (FIT+) under CRCSP, around 10% were not detected to have any pathology by colonoscopy which might explain the positive FIT results, such as polyp, colorectal cancer (CRC), colitis, vascular lesions etc.

3. This has led to a question whether all participants with positive FIT but colonoscopy-negative result should be advised to receive further

investigation by oesophagogastroduodenoscopy (OGD) as a routine to detect upper gastrointestinal (UGI) cancers.

4. FIT detects faecal haemoglobin (Hb) in stool using specific antibodies that react with the globin chain of haemoglobin. Since Hb degrades along the GI tract, FIT is less likely to be positive in patients with UGI tract lesions, and is considered specific for lower GI tract bleeding. Thus, FIT positive result would not be a sensitive indicator for detecting UGI cancers or clinically significant lesions [4].

5. However, routine further investigation for the UGI tract in subjects with positive faecal occult blood result has been controversial and there are no relevant local guidelines regarding the role of OGD in FIT+ subjects with negative colonoscopy findings under routine CRC screening. This paper provides a review on the latest scientific evidence and overseas recommendations regarding UGI tract workup for FIT+ screenees with negative colonoscopy findings as well as relevant local data.

Review of research evidence on the incidence of UGI cancers among CRC screening participants with positive FIT and negative colonoscopy findings

6. Databases were searched for studies reporting UGI lesions in FOBT+ and subjects undergoing colonoscopy with negative findings from 2004 to Oct 2024 inclusive. A total of 7 relevant research papers including 3 systematic reviews[1,2,3], and 4 cohort studies[4,5,6,7] have been identified and summarised below (please refer to appendix I for the summary table).

7. A systematic review examining the use of opportunistic OGD in

FIT+ patients without CRC was published in 2023[1], which included 4 studies of FIT+ patients who underwent either concurrent OGD and colonoscopy or post-colonoscopy OGD. It was found that the incidence of gastric cancer was low at 0.5% (3 gastric cancer of 605 patients and no other UGI cancers were identified). Though there was high prevalence of non-malignant lesions detected by OGD including gastritis, H. pylori-positivity, and gastric polyp in 53%, 16% and 4% of pooled FIT+/colonoscopy-negative patients respectively, the significance of earlier detection of these lesions was not well measured. Given the low incidence of gastric cancer in these patients, there was limited overall evidence to recommend routine OGD as a cost-effective screening measure for all FIT+ patients following a colonoscopy. Instead, opportunistic OGD may be considered based on clinical judgement and individual conditions.

8. In a systematic review and meta-analysis of 21 studies published in *Gastrointestinal Endoscopy* in 2023[2], the pooled prevalence of UGI cancers among FOBT+ patients with negative and positive colonoscopy findings was 0.8% (95%CI=0.3-1.8) and 0.9% (95%CI=0.3-2.3%) respectively, both below 1% which was similar to findings of other studies. The pooled prevalence of non-malignant UGI clinically significant lesions (CSL; lesions potentially explaining occult blood loss e.g. *Helicobacter Pylori.* gastritis, polyps, peptic ulcer, gastritis, vascular disease) among FOBT+ patients with negative and positive colonoscopy findings was 24.8% (95%CI=16.0-36.3) and 32.5% (95%CI=17.6-52.1) respectively and the difference was not statistically significant (P=0.137). On the other hand, it was found that anemia in FOBT+ subjects was associated with UGI

cancers (OR, 6.3; 95% CI 1.3-31.5). This is in line with other studies that clinical factors such as presence of anemia should be considered before further UGI evaluation. This study concluded that while same-day gastroscopy at time of colonoscopy can reduce marginal costs, further appropriately designed prospective studies with cost-effectiveness analyses should be conducted before clinical guidelines can be refined.

9. In a systematic review of 9 studies which identified patients who were FOBT positive and colonoscopy negative[3], OGD was found to have a low yield for UGI cancer, generally 1% or less, even in symptomatic or severely anemic patients. The yield for detecting nonmalignant findings potentially contributing to a positive FOBT was 7% to 19% among asymptomatic patients, while the yield for incidental findings unlikely contributing to a positive FOBT was 10% to 36%. The study concluded that the evidence was insufficient to recommend for or against routine OGD as a means of detecting gastric or esophageal cancers for patients who are FOBT positive/colonoscopy negative, in a population-based CRC screening program. The decision to perform OGD should be individualised and based on clinical judgement.

10. In a Dutch retrospective data linkage study published in 2018[4], participants in a CRC screening programme rolled out in the west of the Netherlands from 2006 to 2012 who developed oral or UGI cancers within 3 years after a positive or negative FIT result were identified through linkage with the National Cancer Registry. No significant difference in incidence was found among the 3 groups: (1) FIT+ and colonoscopy-negative; (2)

FIT+ and colonoscopy-positive; and (3) FIT-negative. The incidence of gastric or esophageal cancer was also very low in FIT+ patients with negative colonoscopy results, where only 2 esophageal cancers and no gastric cancers were diagnosed among 1 367 participants (0.15%), i.e. the hypothetical number needed to scope with OGD to detect 1 gastric or esophageal cancer in this group of participants is 684. This study concluded that it was not recommended to perform routine OGD in FIT+ patients with or without positive colonoscopy findings in the absence of symptoms and risk factors. Based on the low incidence of gastric or esophageal cancer, implementing additional OGD will reduce the cost effectiveness of CRC screening.

11. Following the above study, a more recent study was conducted and published in 2024 based on data from the Dutch national CRC screening participants from 2014 to 2018[5]. The cumulative incidence of "OGD-detectable cancers" (including esophageal, gastric and duodenal cancers) was 0.4%, 0.4% and 0.2% for FIT+ and colonoscopy-negative, FIT+ and colonoscopy-positive, and FIT-negative group respectively. There was no statistically significant difference (p=0.637) in the incidence of OGD-detectable cancers identified among FIT+ screenees compared with FIT- screenees. Considering the overall low cumulative incidence of OGD-detectable cancers as well as the large number needed to scope by OGD, and that OGD is not perfectly sensitive for OGD-detectable cancers, this study concludes that performing OGD in all FIT-positive screenees could not be justified.

12. In an Italian study published in 2007[6], the gastric cancer incidence in an age cohort of 40-74 at first CRC screening from 1985 to 2001 who performed Fecal Occult Blood Test (FOBT) followed by colonoscopy was compared with the expected incidence rates of gastric cancer based on data from the Tuscany Cancer Registry, to generate standardised incidence rates (SIR). In this study, guaiac FOBT was used until 1995 and thereafter replaced by immunochemical FOBT. Statistically significant increase in gastric cancer risk (SIR=146.7; 95%CI=105.8-203.4) was identified in FOBT+ patients with negative colonoscopy results. Gastric cancer incidence was also increased in FOBT+ subjects with positive colonoscopy results (SIR = 121.8; 95% CI 80.9–183.3) with 3-year follow-up but not at a statistically significant level, while the incidence was stable over time in FOBT− subjects. However, the predicted benefit of routine UGI tract investigation would still be low due to low incidence of gastric cancer in FOBT+ patients with negative colonoscopy results within 3 years (0.4%). Assuming 100% sensitivity of UGI tract endoscopy for gastric cancer, the positive predictive value (PPV) of routine UGI tract endoscopy would be 0.4% and the number needed to scope with OGD to detect 1 gastric cancer would be 254. It was concluded that routine UGI tract endoscopy in this specific group of patients is unlikely cost-effective, therefore specific risk factors and symptoms should be considered for selection of appropriate patients for further UGI workup.

13. Similarly, in a Korean study published in 2020[7], the risk of developing proximal cancers within 1, 2, and 3 years after FIT was compared among three groups of participants: FIT-negative participants,

FIT-positive participants who were not diagnosed with CRC after FIT (FIT+/CRC-), and FIT-positive participants who were diagnosed with CRC after FIT (FIT+/CRC+). It was found that the risk of developing esophageal, stomach, and small intestine cancers, as well as overall proximal cancers within 3 years after FIT were higher in both FIT+/CRC- (adjusted OR=1.31; 95% CI=1.27-1.36) and FIT+/CRC+ participants (adjusted OR=1.48; 95% CI=1.33–1.64) compared with FIT-negative participants. However, because the incidence of UGI cancers among FIT+/CRC- participants was very low, the positive predictive value of FIT for proximal cancers in FIT+/CRC- participants was thus very low (0.08%, 1.07%, and 0.02% for esophageal, stomach, and small intestine cancers within 3 years after FIT respectively). Given the high numbers needed to scope to detect one case of UGI cancer, routine OGD for all FIT+/CRC- patients was not justified. Instead, other clinical factors should be considered for predicting UGI cancer risk, which may allow better selection of subjects for UGI evaluation.

Review of overseas guidelines on providing OGD to CRC screening participants with positive FIT and negative colonoscopy findings

14. Review on international practice, overseas clinical guidelines and screening protocols have also been conducted. The U.S. Multi-Society Task Force on CRC suggested in the 2017 Consensus Statement that in the absence of symptoms or signs of UGI disease, positive FIT and negative colonoscopy results should not prompt UGI assessment[8].

The UK's bowel cancer screening protocol states that after performing colonoscopy, even if no polyps are found, no further investigation is needed at this time[9]. Canadian Association of Gastroenterology position statement on screening individuals at average risk for developing colorectal cancer: 2010 stated that upper endoscopy is not required in every case when a negative colonoscopy is the result of a positive FOBT. A decision to perform upper endoscopy should be based on clinical judgment and individualised to patient history and findings[10]. Lastly, in a systematic review[11] summarising the current global CRC screening guidelines for average risk adults, there were no recommendations on performing routine UGI endoscopy for colonoscopy-negative individuals during screening.

Local data on incidence of UGI cancers among FIT-positive and colonoscopy-negative CRCSP participants

15. The FIT+ and colonoscopy-negative cases under CRCSP from 2017-2019 (born in 1942-1963) were identified and sent to the Hong Kong Cancer Registry for linkage in order to identify the incidence of UGI cancer among this group of participants.

16. Participants who have collected faecal samples within 2017-2019 with a positive FIT result were included in the study. Colonoscopy-negative cases were defined as FIT+ cases with no pathology which might explain the positive FIT results (such as polyp, adenocarcinomas, colitis, vascular lesions etc.) identified during colonoscopy examination. UGI cancers were defined as cancers in esophagus, stomach, duodenum, which

can be detected by OGD.

17. A total of 18 243 participants had positive FIT in 2017-2019 and underwent colonoscopy. Among these participants, 2 468 (13.5%) had negative colonoscopy findings. Within 3-year follow up period (2020-2022), 4 cases of UGI cancers were identified by Hong Kong Cancer Registry, resulting in a cumulative incidence of approximately 0.16% (4 out of 2 468). This concurs with the less than 1% incidence of UGI cancer among FIT+ and colonoscopy-negative cases reported by many overseas studies.

18. For comparison, the cumulative incidence of UGI cancers in the general population of the same birth cohort (i.e. born in 1942-1963) was approximately 0.17% (number of cases = 3 304; average birth cohort size = 1 934 000), which was similar to 0.16% in the FIT+ and colonoscopy-negative group under CRCSP.

Summary

19. Findings of relevant overseas studies indicated that detection rates of UGI cancers among CRCSP screenees with FIT+ but colonoscopy-negative result were relatively low and were comparable to that of screenees with FIT+ and colonoscopy-positive result. In view of the relatively low detection rate and positive predictive value for UGI cancers, there is no evidence supporting routine OGD screening in FIT+ screenees as an effective or cost-effective measure for prevention of UGI

cancers.

20. Though studies indicated high prevalence of non-malignant UGI lesions (such as H. Pylori-positivity, gastritis, polyps etc) among FIT+ screenees (including both colonoscopy-negative and colonoscopy-positive groups), there was no evidence supporting that routine screening by OGD for early detection and treatment of these asymptomatic lesions would have overall benefit and reduce mortality. Although an UGI endoscopy might not pose high procedural risk to an individual, the overall burden imposed by performing routine OGD for all FIT+ and colonoscopy-negative CRCSP screenees at a population level could be substantial. There is also a lack of data which demonstrate the cost-effectiveness of performing UGI endoscopy in this group of patients.

21. Apart from the above, relevant overseas guidelines and screening protocols for CRC screening programmes do not recommend performing routine OGD for CRC screenees with FIT-positive but colonoscopy-negative results.

22. Findings of local CRCSP was in line with results of overseas studies. The cumulative incidence rate of UGI cancers among CRCSP screenees with FIT-positive but colonoscopy-negative results was low and comparable to that of general population.

Conclusion

23. There is insufficient evidence supporting routine OGD as a cost-effective measure for all FIT+ and colonoscopy-negative CRCSP participants. In the absence of symptoms or signs of UGI diseases, positive FIT and negative colonoscopy results should not prompt routine OGD. The decision to perform OGD should be individualised according to patient's clinical condition including symptoms and signs suggestive of UGI diseases as well as other risk factors.

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Appendix I

Ref. no.	Title of the paper	Year of publication	Study design	Sample size/ No. of included studies	Type of FOBT	Definition of negative colonoscopy	UGI cancer incidence in FIT+ and colonoscopy-negative group	UGI benign lesions / CSL incidence in FIT+ and colonoscopy-negative group	Remark
1	Gastroscopy after positive screening for faecal immunochemical tests and colonoscopy: A systematic review.	2023	Systematic review	605 / 4 studies	FIT	Variable between included studies	0.5% (3 out of 605)	Incidence of gastritis, HP+, gastric polyp: 53%, 16%, 4% respectively	-
2	Upper GI endoscopy in subjects with positive fecal occult blood test undergoing colonoscopy: systematic review and meta-analysis.	2023	Systematic review and meta-analysis	6 993 FOBT subjects/ 21 studies	6 studies used FIT, 11 used gFOBT; 4 not specified	Variable between included studies	0.8%	24.8%	Anemia in FOBT+ subjects was associated with UGI cancers (OR, 6.3; 95% CI 1.3-31.5)
3	Gastroscopy following a positive fecal occult blood test and negative colonoscopy: systematic review and guideline	2010	Systematic review	4763 FOBT+ /col-neg, patients / 9 studies	FIT / gFOBT	Variable between included studies	3 studies: 0 case 3 studies: <1% 1 study: 7% 2 study: Not applicable	Among asymptomatic patients, Yield for nonmalignant findings potentially contributing to a positive FOBT was 7% to 19%;	-

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								Yield for incidental findings unlikely contributing to a positive FOBT was 10% to 36%.	
4	Risk of oral and upper gastrointestinal cancers in persons with positive results from a fecal immunochemical test in a colorectal cancer screening program. (Dutch)	2018	Cohort study	1 367 (FIT+ and colonoscopy-)	FIT	Colonoscopy without a diagnosis of advanced neoplasia (advanced adenoma or CRC)	0.15% (2 esophageal cancers among 1,367 participants)	Not specified	No statistically significant difference among 3 groups: 1. FIT+ Col negative; 2. FIT and Col+; 3. FIT negative
5	Risk of cancers proximal to the colon in fecal immunochemical test positive screenees in a colorectal cancer screening program. (Dutch)	2024	Cohort study	50 661 (FIT+ and colonoscopy-)	FIT	No advanced neoplasia (CRC or advanced adenoma)	OGD-detectable cancer 0.4%	Not specified	No statistically significant difference among 2 groups: 1. FIT+ Col negative;

Ref. no.	Title of the paper	Year of publication	Study design	Sample size/ No. of included studies	Type of FOBT	Definition of negative colonoscopy	UGI cancer incidence in FIT+ and colonoscopy-negative group	UGI benign lesions / CSL incidence in FIT+ and colonoscopy-negative group	Remark
									2. FIT and Col+
6	Gastric cancer after positive screening faecal occult blood testing and negative assessment. (Italy)	2007	Cohort study	3 555 (FOBT+ and colonoscopy-)	Guaiac FOBT (1985-1995); FIT (1995-2001)	no colorectal neoplasm (cancer or adenoma)	0.4% (14 gastric cancers within 3 years)	Not specified	No statistically significant difference among 2 groups: 1. FIT+ Col negative; 2. FIT and Col+;
7	Positive Fecal Immunochemical Test Results Are Associated with Increased Risks of Esophageal, Stomach, and Small Intestine Cancers. (Korea)	2020	Cohort study	368 553 (FIT+ and CRC-)	FIT	Not applicable	0.08%, 1.07%, and 0.02% for esophageal, stomach, and small intestine cancers respectively within 3 years	Not specified	OR for developing proximal GI cancer= 1.31 among FIT+/CRC- 1.48 among FIT+/CRC+ compared to FIT negative participants

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