CT for Double Lung and Colorectal Cancer Screening

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Annual screening of lung cancer (LC) with chest low-dose computed tomography (CT) and screening of colorectal cancer (CRC) with CT colonography every 5 years are recommended by the United States Prevention Service Task Force.

chest CT computed tomography CT colonography

1. Introduction

The 2021 statements of the United States Prevention Service Task Force (USPSTF) have recommended both chest low-dose computed tomography (LDCT) for Lung Cancer (LC) screening and CT colonography for colorectal cancer (CRC) screening [1][2]. This justifies consideration of the opportunity for a single-appointment CT for double screening of LC and CRC. However, importantly, while chest LDCT is the only recommended screening tool for LC since 2013, other screening tools besides CT colonography have also been recommended for CRC since the late 1990s [1][2].

2. Epidemiology

LC and CRC are among the most common and lethal neoplasms, accounting for about 2 and 1.8 million cases and 1.7 and 0.8 million deaths per year worldwide, respectively [3]. Accordingly, the overall 5-year survival rate of LC is 20.5% [4], and that of CRC is 73.7% [5]. Together, LC and CRC account for about 1/5 (21.8%) of all cancer cases and 1/4 (27.6%) of all cancer deaths [3].

Since early stage LC has a better prognosis and is more amenable to treatment than more advanced-stage LC [1], and removal of precancerous lesions halts the progression from polyp to CRC [2], screening of LC and CRC can save lives and is fully justified as a health preventive intervention.

LC has sporadic distribution and cigarette smoking, a modifiable behavior, is its main key risk factor, along with age [1]. The proportion of deaths from LC attributable to smoking is 76% among males and 39% among females [6]. Additional risk factors for LC include second-hand smoke, environmental (radon, domestic fuel smoke, outdoor air pollution) and professional (asbestos, ionizing radiations, chromium, arsenic, etc.) exposures, infections and chronic inflammations, including Chronic Obstructive Pulmonary Disease (COPD) and Interstitial Lung Disease

(ILD) [1][7][8][9][10]. Worldwide, 15–20% of men and around 50% of women with LC, particularly in Asia, are never smokers, whereas in the US, 9% of men and 19% of women with LC are never smokers [11][12].

Notably, several studies have demonstrated that selection of subjects to be invited to LC screening based on age and pack years only, as indicated by the USPSTF, performs worse in terms of predicting LC risk, and hence are suboptimal for subjects selection compared to personal risk prediction calculation models, which consider additional risk factors such as history of respiratory diseases, previous malignancy, family history of lung cancer (first-degree relative diagnosed at age 60 years or younger), and exposure to asbestos [13][14]. So far, the modified Liverpool Lung Project [LLPv2] and Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [PLCO] models [15][16] have been those more frequently utilized to select patients for LC screening in a clinical trial.

CRC too has a predominantly sporadic distribution, but familial history of the disease is present in 20–30% of cases, and rare inherited diseases such as Lynch Syndrome and Familial Adenomatous Polyposis and others are observed in 6–10% of cases, [17]. Age, race and history of inflammatory bowel disease (ulcerative colitis and Crohn's colitis) are additional non-modifiable risk factors for CRC. However, several modifiable lifestyles and environmental risk factors are now also known for colon polyps and CRC [17], including diet—in particular, high intake of red and processed meat [18]—smoking, alcohol intake, little physical activity and elevated body mass index. Subjects with family history, the above inherited diseases or with inflammatory bowel disease are considered at "high-risk" of CRC and must be distinguished from the remaining subjects who are considered at "average-risk".

Increased smoking habit is responsible for a growing trend of LC incidence and mortality in women, whereas these are decreasing in men [19]. An unexplained increase worldwide in rates of CRC in individuals under 50 has been recently described [17].

3. Pathology

In general, early stage tumors and precancerous lesions are the target of screening procedures.

In the lung, only Non-Small Cell Lung Cancer (NSCLC) shows the relatively low growth compatible with screening, which affords its detection in early stages (I and II) when it can be surgically removed and definitely cured. Unfortunately, this is not the case for the fast-growing Small Cell Lung Cancer (SCLC), which accounts for 15–20% of primary lung tumors. SCLC escapes screening, and no benefit of its detection in the screening setting was reported in terms of decreased mortality [20]. Among the screen-detected NSCLC, adenocarcinoma and squamous carcinoma are the most frequent [21][22][23][24]. Adenocarcinoma is particularly frequent in women, and its long sojourn time [25] is associated with a more marked decrease in LC mortality following LDCT screening in women than in men [21][23][24][26].

Precancerous lesions in the lung can be distinguished into those related to adenocarcinoma and those related to squamous cell carcinoma. The former typically appear as a peripheral lung nodule, are easily demonstrated by chest LDCT and include (1) atypical adenomatous hyperplasia and (2) several distinct conditions that have

replaced the old comprehensive term bronchoalveolar carcinoma (BAC) as adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma and invasive mucinous adenocarcinoma [27]. The CT correlates of these histologic entities vary from lung nodules with pure ground glass (non-solid) density to mixed (part solid) and solid density (see below). Dysplastic lesions of the central airways which are precursors of squamous cell carcinoma are well detected by fluorescence bronchoscopy [28] and can escape chest LDCT.

From a histological point of view, CRC is usually an adenocarcinoma (86% of all colon cancers- others include adenosquamous carcinoma, squamous cell carcinoma, spindle cell carcinoma, undifferentiated carcinoma and other special histopathological types) and arises from two precancerous lesions, namely adenomatous polyps, underlying 60–70% of CRC, and sessile serrated lesions, accounting for about 15–30% of CRC [17], which can coexist in the same subject, but have a distinct aspect at optical colonoscopy. In fact, at optical colonoscopy, adenomatous polyps appear to be well-demarcated lesions variably elevated on a stalk or pedicle. Sessile serrated lesions are flat with indistinct margins, and may show a “mucus cap” that makes them more likely to be missed on optical colonoscopy compared to adenomatous polyps.

4. Screening Tests for LC and CRC, Their Organization and Adhesion

The National Lung Screening Trial in the US demonstrated that, unlike chest X-rays, screening with chest LDCT reduces mortality from LC by 20% in smokers and former smokers [21]. In a recent metanalysis of nine trials, LDCT screening was associated with a 16% relative reduction in LC mortality when compared against a non-screening LDCT control arm [29].

Accordingly, annual LDCT screening of LC is recommended by USPSTF for subjects aged 50–80 years with a smoking history of at least 20 pack years or who have quit in the last 15 years [1]. Experience with LC screening in never smokers is limited to a single study in Asia [30], but the positive results in terms of early stage cancers detection represent an area of further research and debate [31]. Screening in asbestos-exposed workers is effective in detecting asymptomatic LC [32]. Adoption of a validated risk stratification approach is recommended by the European Union (EU) Position Statement to implement LC screening in Europe [33].

Several screening tools are available for CRC and its precursor that is the advanced adenoma [34][35][36][37][38]. They include stool-based methods (high-sensitivity guaiac fecal occult blood testing (HSgFOBT) annually, fecal immunochemical testing (FIT) annually and multi-target stool DNA every 1 to 3 years), CT colonography, flexible sigmoidoscopy (FS) and optical colonoscopy (OC), but also barium enema, blood-based tests and colon capsule endoscopy [17]. However, only stool-based methods, CT colonography, flexible sigmoidoscopy and optical colonoscopy have been recommended as screening tools [2][39][40].

So far, the effect of screening in decreasing the CRC incidence and mortality has been demonstrated for stool-based methods [17][41] and for FS [42][43], whereas it is lacking for CT colonography and OC.

According to modeling studies, implementation of screening would yield about a 50% decline in CRC incidence and mortality [44][45].

As a matter of fact, the USPSTF recommends screening without identifying a preferred option [2]. In average-risk individuals, recommended screening intervals for CRC depend upon the screening tool and range from one year for stool-based methods to 5 years for CT colonography and FS, to 10 years for OC [2]. In average-risk individuals, the USPSTF recommends CRC screening from 45 to 75 years of age, whereas it can selectively be requested by physicians in subjects aged 76–85 years who had never experienced screening or whose life expectancy is 10 years or more [2]. Advocates of CT colonography [46][47] purport that it is an efficient, underused screening tool for CRC that is intermediate for invasiveness between stool-based methods and OC, while it exhibits a detection rate for advanced adenoma that is higher than stool-based methods and similar to FS or OC. In fact, randomized screening trials showed that CT colonography has higher detection rate for advanced neoplasia (5.2%) than one FIT round (1.7%) [35], and a similar detection rate of flexible sigmoidoscopy [5.1% for CT colonography vs. 4.8% for flexible sigmoidoscopy] [36].

In individuals at high risk of CRC development, it is recommended that screening begins earlier, at age 40 or 10 years before the youngest age of CRC diagnosis in the family [48], and no indication is established concerning the screening tool and interval. However, since OC affords both detection and removal of polyps and adenomas in a single examination, CRC screening in people at high risk must be performed with OC [17][49][50][51] and should be performed every two years or annually [52][53].

Screening can follow two basic modalities: opportunistic or organized-population based. Opportunistic screening usually is based on the individual desire to perform search of pre- or early cancer conditions and on an ad hoc or fee-based service, while population-based organized screening is generally supported by the public health service and entails invitation of a target population and measurement and reporting of screening quality [17].

LC screening has been recommended by the USPSTF since 2013 [54], while its implementation as a population-based screening is currently investigated in many European countries. CRC screening using stool-based methods started in around 1996 [55][56] and using OC in 1997 [17], and is predominantly opportunistic in the US, whereas many European countries have implemented population-based CRC screening.

A general problem of screening initiatives is low adherence, which can jeopardize their efficacy. Adhesion to LC screening is variable and, despite the USPSTF recommendations for annual LDCT screening since 2013, it involved only 17% of the target population in a recent survey in the US, with a non-significant lower participation of non-Hispanic Black individuals [57]. In case of CRC screening, the adherence of average-risk people varies with the screening tool and is higher (55–68%) for FIT and other stool-based modalities [35][37][38], and lower for FS (27–52%) [36][37], CT colonography (25–34%) [34][35][36] and OC (22–35%) [34][38]. Independently from the screening tool, overall adherence to CRC screening in the US is still below 70% in most geographical regions (Centers for Disease Control and Prevention. United States cancer statistics colorectal cancer stat bite. 2020. https://www.cdc.gov/cancer/uscs/about/stat-bites/index.htm, accessed on 30 June 2022). The following

interventions to increase the suboptimal CRC screening uptake have been identified: outreach, navigation, education of patients or providers, reminders and financial incentives [17]. It is also conceivable that the opportunity to perform double screening in a single session CT might exert a drag effect on CT colonography in smokers and former smokers undergoing chest LDCT for LC screening, at least in an opportunistic framework.

For both LC and CRC screening, adhesions were reduced for a variety of reasons during the COVID-19 pandemic [58]. In Italy, participation rate in the population-FIT-based CRC screening was 42% in 2019 and 34% in 2020, with a 2019–2020 gap of 1.1 million tests due to the COVID-19 pandemic [59].

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