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Diagnostic protocols in oncology: workup and treatment planning. Part 1: the optimitation of CT protocol

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Abstract. – The increase in oncology knowledge and the possibility of creating personalized medicine by selecting a more suitable therapy related to tumor subtypes, as well as the patient's management with cancer within a multidisciplinary team has improved the clinical outcomes. Early detection of cancer through screening-based imaging is probably the major contributor to a reduction in mortality for certain cancers. Nowadays, imaging can also characterize several lesions and predict their histopathological features and can predict tumor behaviour and prognosis. CT is the main diagnostic tool in oncologic imaging and is widely used for the tumors detection, staging, and follow-up. Moreover, since CT accounts for 49-66% of overall patient radiation exposure, the constant reduction, optimization, dose inter- and intraindividual consistency are major goals in radiological field. In the recent years, numerous dose reduction techniques have been established and created voltage modulation keeping a satisfactory image quality. The introduction of CT dual-layer detector technology enabled the acquisition of spectral data without additional CT x-ray tube or additional acquisitions. In addition, since MRI does not expose the body to radiation, it has become a mainstay of non-invasive diagnostic radiology modality since the 1980s.

Key Words:
Computed tomography, Radiation exposure, Oncologic imaging, Magnetic resonance study, Abbreviated protocol.

Introduction

Computed tomography (CT) is the main diagnostic tool in oncologic imaging, and it is widely used for tumors detection, staging and follow-up[1-6]. Although only 9% of all radiological examinations are CT, they contribute to up to 65% of the medically induced radiation exposure[7]. CT accounts for 49-66% of overall patient radiation exposure, and this topic has recently led to new regulations in the European Union *via* the EURATOM directive[7,8]. Consequently, the constant reduction, optimization, inter- and in-

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traindividual consistency of dose are main goals in radiological field. An important aspect of dose optimization stems from the constant need for image quality during subsequent CT exams, to reliably assess the tumor's response to treatment, ensuring the lowest reasonably achievable exposure levels (ALARA principle)[9].

In the recent years, several dose reduction techniques have been developed, such as the automatic tube current modulation (ATCM) that regulates the tube current and represents one option to reduce radiation dosemaintaining image quality[9,10] and the tube voltage modulation that presents another option to reduce the dose keeping a satisfactory image quality[11,12]. For image reconstruction, the standard filtered back projection (FBP) methods are replaced by iterative reconstruction algorithms able to reduce radiation maintaining high image quality[13,16].

The introduction of CT dual-layer detector technology enabled the acquisition of spectral data without additional CT x-ray tube or acquisitions. Dual-layer spectral CT (DLCT) acquisitions allow material decomposition (virtual non-contrast, iodine-only imaging, and effective atomic numbers), as well as the virtual monoenergetic images calculation. Several clinical studies[17,18] have already been performed showing the DLCT advantages for head, thoracic, vertebral and abdominal districts. However, for the image acquisition, a tube potential of either 140 kVp or 120 kVp is necessary to allow spectral decomposition under the energy-specific x-ray exploitation of absorption of different materials. In contrast to tube current changes, tube potential changes have a non-linear effect on radiation dose: in comparison to 80 kVp, the x-ray tube output (i.e., air kerma or exposure) is 1.5 times higher for 100 kVp, 2.5 times higher for 120 kVp, and 3.4 times higher for 140 kVp[19-21]. No radiation dose increase is necessary for dual-source, dual-energy scans without compromises in image quality of the thorax and abdomen[19-21]. In contrast, Singh et al[22] showed dose equivalence to dual-source, dual-energy acquisition but with inferior image quality, whereas other authors state that rapid voltage switching acquisition resulted in higher patient's radiation.

The administration of intravenous contrast media (CM) is an integral element of many CT examination protocols. However, CM administration is also accompanied by a potential risk for adverse reactions, in particular, allergic reactions[23] and contrast-induced nephropathy[24]. Therefore, CM administration should be scrutinized, and the lowest adequate dose should be used[25]. In order to address this problem, several studies[26-28] have shown that the CM amount can be reduced using lower tube voltages. In the last decade, by using DLCT, some scholars[29] have reported CM dose reductions of 50% preserving image quality. Consequently, a DLCT protocol with reduced CM should be implemented.

Magnetic resonance imaging (MRI) is one of the non-invasive imaging techniques that have superior soft tissue contrasts and potential physiological and functional applications[30-35]. Moreover, MRI does not expose the body to radiation. Technical advances in MRI have improved image quality and have led to expanding clinical indications[36-38]. However, long examination and interpretation time, as well as higher costs, still represent barriers to MRI use[39]. Abbreviated MRI protocols have emerged as an alternative to standard MRI protocols[39]. These abbreviated protocols seek to reduce longer MRI protocols by eliminating unnecessary or redundant sequences that negatively affect cost, examination time, patient comfort, and image interpretation time. Abbreviated protocols have been used successfully for hepatocellular carcinoma screening, for prostate cancer detection, and for screening for non-alcoholic fatty liver disease, as well as monitoring patients with this disease[40-45]. Nevertheless, multiple applications still need to be explored in the abdomen and pelvis.

The purpose of this narrative review is to report an update on the oncologic patients CT protocols, with regard to the optimization of the contrast medium dose and radiation dose, as well as the state of the art of the abbreviated MRI protocols. In addition, we described the latest knowledge in the field of artificial intelligence (AI) in the daily radiological practice to optimize studies protocol.

Imaging and Cancer

The increase in knowledge in oncology and the possibility of creating personalized medicine by selecting a more appropriate therapy related to the different tumor subtypes, as well as the management of patients with cancer within a multidisciplinary team, has improved the clinical outcomes[46-48]. The main features to be considered are the most appropriate surveillance for the patient at risk for cancer, early diagnosis, improvement in the efficacy of therapies based on better patient selection[49-53] and, the possibility of

identifying responders or non-responders to therapies as soon as possible[54-56]. Medical imaging comprises a huge number of imaging techniques, and multiple biomedical imaging techniques are used in all phases of cancer management because they are able to provide morphological and functional data[57-60]. Early detection of cancer through screening based on imaging is probably the major contributor to a reduction in mortality for certain cancers[61]. Nowadays, imaging can also characterize several lesions, predict their histopathological features so as several radiological features can correlate with prognosis[62-64].

Imaging is the tool by which tumors of the gastrointestinal tract are staged. Moreover, it is used for treatment assessment and follow-up[65-69]. Unlike, for hepatic tumors (primary or secondary), as well as for pancreatic lesions, it also has a role for detection and characterization[70-74]. In lung and breast cancers, imaging techniques are involved in the phases of characterization, staging, treatment assessment and follow-up phases[75-78], so as they represent the recognized screening tools[79-82].

Diagnostic Workup and Treatment Planning in Lung Cancer

Lung cancer is one of the most common cancer, remaining the biggest killer[82,83]. With an estimated 2.2 million new cancer cases and 1.8 million deaths, lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in 2020, representing approximately one in 10 (11.4%) cancers diagnosed and one in 5 (18.0%) deaths. Lung cancer is the leading cause of cancer morbidity and mortality in men, whereas, in women, it ranks third for incidence, after breast and colorectal cancer, and second for mortality, after breast cancer[83,84].

Multidisciplinary diagnostic assessment is essential in the screening, diagnosis and follow up of the patients at risk or with lung cancer[84]. Radiologists have a central role in the diagnostic management and have to ensure appropriate image quality with minimum radiation dose. Current guidelines of the America College of Radiology (ACR) recommend the use of CT with 16 or more detectors and slice thickness of 2.5 mm or less, with 1-mm thickness preferred. In this context, great efforts are currently being made by CT manufacturers to reduce the dose and maintain diagnostic quality. Technologies, such as automated exposure control, lower tube current and iterative reconstruction, were recently introduced, enabling further dose decrease for chest CTs. Moreover, the concept of 'ultra-low dose (ULD) CT' (or submillisievert CT) delivers a radiation dose approaching that of two chest X-ray (CXR) views at the cost of a slight deterioration of the image quality[85]. Among these technological advances, the most significant is probably the new iterative reconstruction whether full iterative or hybrid. Also, several features can influence the radiation dose directly or indirectly which can result in safe dose reduction without affecting image quality. First and foremost, it should be stated that radiation dose to the patient can be significantly reduced by carefully following proper techniques, such as: *a*: correct patient centering by placing the chest in the center of the field of view (FOV), *b*: reduce unnecessary scan length, *c*: shielding radiosensitive targets, such as the mammary gland, and *d*: organ-based tube current modulation[85]. The scanning parameters employed in the detection of ground glass opacities (GGO) and consolidation involve: *a*: modification of tube current, that represents the simplest approach to reduce radiation dose; *b*: employing 100 kVp protocol can reduce radiation dose by 44% while maintaining low-contrast detectability compared with a 120 kVp protocol; *c*: a correct patient centering to obtain an optimal performance of the automatic exposure control with tailored according to patient weight, and *d*: employing iterative reconstruction with low kVp is that of those when scanning with 120 kVp with the sensitivity to detect GGO, ground-glass nodules and interstitial opacities decreased significantly, from 89% to 77%, 86% to 68% and 91% to 71%, respectively (all p-values < 0.00001)[85]. These newer radiation-reduction technologies and protocol optimization allow even greater dose reductions from 3 mGy to less than 0.3 mGy. Automatic exposure control systems, which change tube output at different anatomic locations during scanning depending on tissue attenuation, can be used to adjust dose for patient size. Multiplanar reconstructions can be helpful in determining whether certain solid or GGO are truly nodules or have the linear or flat configuration of atelectasis and scars[85,86]. Current lung cancer screening guidelines use either mean diameter, volume, or density (solid, pure ground-glass, part-solid ground-glass) of the largest lung nodule on the previous CT scan or appearance of a new nodule, as well as the presence of lung cancer risk factors, to ascertain the timing of the next CT o the choice of additional diagnostic testing. Once a follow-up scan is obtained, assessment of growth

can be made. Generally, absence of growth in a solid nodule over a 2-year period makes malignancy unlikely[84].

Screening by low-dose CT is not free of negative effects. Over 90% of nodules are benign, false positives lead to unnecessary further evaluations, such as a lung biopsy or bronchoscopy, which should only be done as a result of screening[87]. Exposure to ionized radiation annually is still a concern, nevertheless after 20 annual screening CT examinations, the increased risk of cancer would be only 0.22% in women and 0.12% in men, relative to the estimated lifetime risk of developing lung cancer among smokers of 15%[88].

Following resection of early-stage lung cancer, patients are at risk of both recurrent disease and development of new primary lung tumors. Observational studies show risk of recurrence for early lung cancer survivors of up to 10% per year in the early years declining to 2% thereafter[89]. To detect these cancer recurrences and to treat early and potentially curable relapses, cancer guidelines suggest follow-up of these patients (Figure 1). According to the guidelines of the European Society of Medical Oncology, follow-up visits should be performed every 6 months for the first 2 years after curative treatment, including history, physical examination and chest CT (optional contrast enhanced) for 2-3 years after definitive surgical treatment for stage I-II lung cancer, followed by annual low-dose non-contrast CT for patients without evidence of disease. After completion of 5-year follow-up, annual visits with surveillance by low-dose chest CT scans are suggested[89]. There is currently no evidence of an added benefit from imaging the abdomen and pelvis following resection early lung cancer[89].

Dual energy CT (DECT) does not play a role in the ongoing lung cancer screening protocols because it requires intravenous contrast injection. DECT can be a useful tool for distinguishing malignant from benign solid pulmonary nodules and lung squamous cell carcinoma from adenocarcinoma by measurement of the

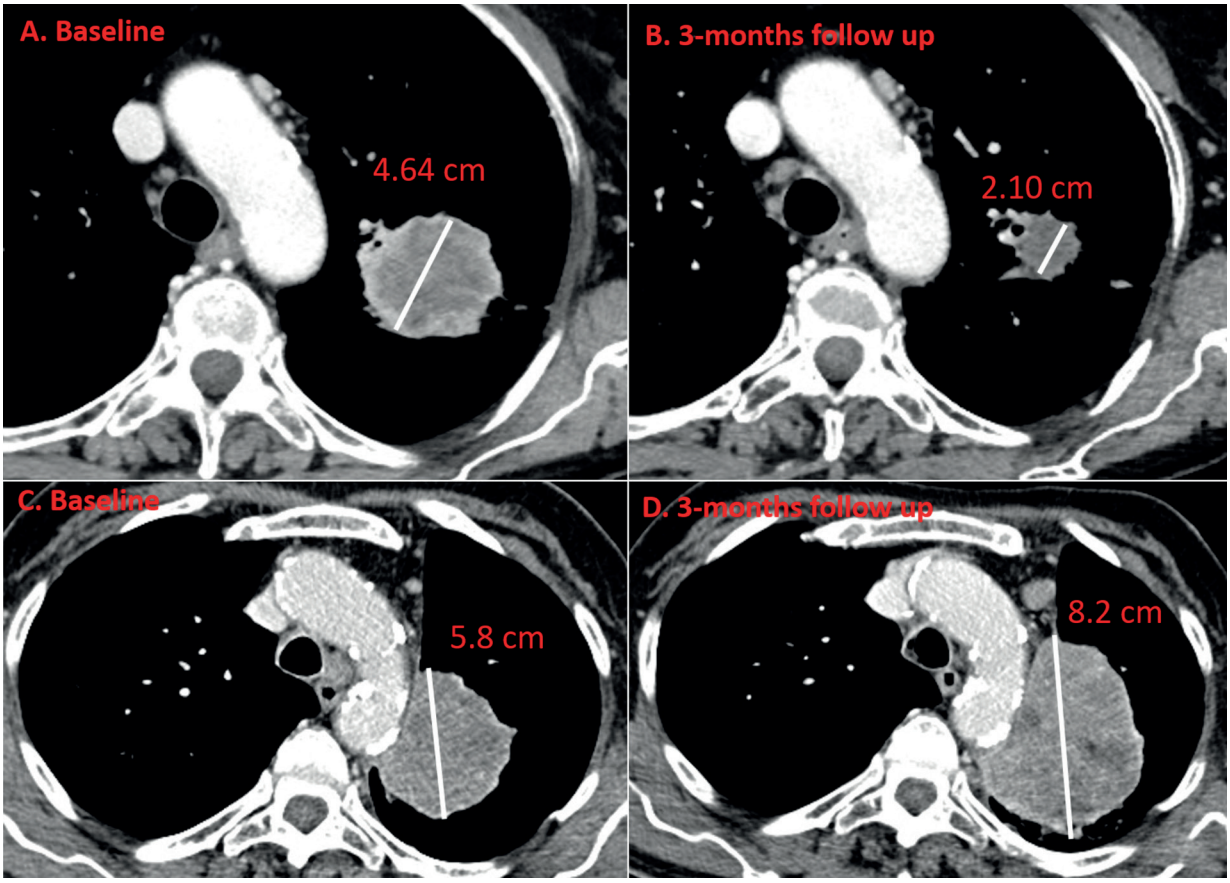

Figure 1. Two examples of follow-up CT in lung cancer radiological assessment: case in **A-B** show a partial responder after chemotherapy, instead case in **C-D** is a progressive disease after 3-months follow-up.

degree of enhancement and detection of calcifications without additional radiation dose. It also could be functional for response evaluation after treatment with anti-angiogenic substances by providing accurate information on the extent of tumor nodules and lymph nodes enhancement, which can be accomplished without obtaining non-enhanced images[90,91]. Another practical use of DECT in oncologic surveillance is related to reduced amount of contrast media by the way of acquisition media low-energy virtual monochromatic images which can enhance the contrast of images, obtained with 30% of the conventional dose of contrast media in patients with kidney disease[91]. However, contrast-enhanced CT is a required tool to detect abdominal-pelvic metastasis and evaluate lung cancer progression before initiating treatment. Pulmonary artery-vein separation CT angiography (PA-PV CTA) to preoperatively evaluate the branches of the pulmonary artery and vein is performed before video-assisted thoracic surgery (VATS) of the lungs[93]. A dual phase CT scan for the pulmonary artery and vein is usually performed. However, one of the major concerns associated with the addition of PA-PV CTA to standard staging CT is the drastic increase in radiation dose. Since patients with early-stage lung cancer, who undergo VATS, are expected to demonstrate long-term survival and undergo repeated diagnostic and follow-up CT examinations, it is imperative that radiologists and radiology technicians consider reducing the radiation dose, maintaining image quality and conform to the "as low as reasonably achievable" principle[92]. To reduce the radiation dose, several research developed the split-bolus single-phase CT scan protocol (split-bolus protocol), in which whole-body staging CT (standard protocol) and PA-PV CTA images can be acquired in a single session[92], showing that the split-bolus protocol is a dose-efficient protocol which enables the staging CT and PA-PV CTA in a single session and provides sufficient image quality for preoperative assessment of patients with lung cancer[92].

Gastric Cancer

Gastric cancer (GC) is the fifth most diagnosed malignancy worldwide and the third most common cause of cancer death globally. The most common risk factors for these conditions include *Helicobacter pylori* infection, age, high salt intake, and diets low in fruits and vegetables, low socioeconomic status, cigarette smoking. Moreover, the incidence of gastric cancer is two times higher in males than females[93]. GC peaks is in the seventh decade of life. Often, a delay in diagnosis may account for the poor outcome, in fact, prognosis is strictly linked to staging at the initial diagnosis and the 5-year and 10-years survival rate is about 31-34% and 52-55% respectively[93]. GC presents vague and multiple symptoms, such as, sudden weight loss, abdominal pain, epigastric fullness, nausea and vomiting, loss of appetite, dyspepsia, dysphagia, indigestion, heartburn, fatigue[93,94].

Adenocarcinomas arising from gastric epithelium are the most common malignancies of the stomach (90% of cases), these ones are mainly found in the gastric cardia (31%), followed by the antrum (26%) and body of the stomach (14%)[93,94]. Tumors deriving from connective tissue (sarcoma) and from lymphatics (lymphoma) are less common. Linitis plastica, a type of adenocarcinoma that diffusely infiltrated the stomach wall, account for the remaining 10%[95].

Currently, contrast enhancement (CE) CT is the workhorse in imaging of GC for Tumor Node Metastasis (TNM) staging, restaging after neo-adjuvant/conversion/or palliative chemotherapy and follow-up (together with oncologic markers: CEA, Ca 19.9, Ca 72.4, Ca 125), due to its availability and high spatial resolution[96,97].

In staging, CECT allows to differentiate between patients who can go straight to surgery and those who need to neoadjuvant therapy; the dividing line between the two groups is represented by patients with $T \geq 3$ with any N or patients with N+ regardless of T. In these cases, pre-surgical chemotherapy is required 9[7,98]. Kim et al[100] reported that overall accuracy of CECT in T-staging is about 82.7%. For GC, surgical exclusion criteria are: presence of more than three hepatic metastases on the same lobe or multiple bilateral liver lesions, pancreatic capsule massively infiltrated, mesenteric root, small bowel, and its mesentery infiltration[100].

A rigorous methodology of the CECT acquisition protocol is essential for evaluation of GC. Gastric distension is required through 500-1000 mL of tap water or oral contrast with effervescent granules; the use of hypotonic agents (1 mg Glucagon) is also recommended and perhaps polyethylene glycol may be used for small bowel distention and to better assess wall infiltration[101]. Gastric distension is necessary for T-parameter delineation, better definition of wall contrast enhancement and assessing infiltrated areas, since

regions affected by cancer do not distend in contrast to disease-free areas[102]. Although the use of tap water is more common due to its availability and prompt use, Giganti et al[103] in their study showed how distension of gastric lumen by air filling is more accurate than by water for the demarcation of regions of interest (ROI), this is especially useful in the further evaluations of texture analysis and quantitative radiomics studies of GC[104-107]. When comparing protocol without and with administration of anti-peristaltic product, many scholars[103] demonstrated that the ROI delineation is more reproducible in the different phases of CT acquisition if hypotonic agent are used. A standard CECT protocol can be employed for both diagnosis and follow-up. Patients can be scanned in the supine position with cranio-caudal apnea scans and should undergo non-contrast and contrast-enhanced CT scanning. Iodinated contrast medium can be injected into the antecubital vein at a flow rate of 3-4 mL/s using an automatic injector, immediately followed by a saline flush (40-50 mL)[103]. Contrast-enhanced triphasic images can be achieved during arterial phase on the upper abdomen (40 seconds) to evaluate the liver, total body portal venous phase (70-80 second) for liver, and also, other distant localizations and late phase (180 second) on the entire abdomen for evaluation not only of the liver but even of possible peritoneal carcinomatosis (Figure 2)[103]. CT also have high performance because it allows thin layer multiplanar reconstructions with coronal and sagittal planes, which are necessary for the proper study of gastric tract and for a meticulous evaluation of the extension of disease[103]. Wang et al[105] demonstrated that DECT plays a role in the staging and re-staging of gastric cancer[105]. With monocromatic beam at low-voltage (40 keV), especially in late post contrast phase (180 second), it is possible to assess peritoneal carcinomatosis; or with iodine maps which underlines the presence of contrast and allows quantitative measurements within peritoneal le-

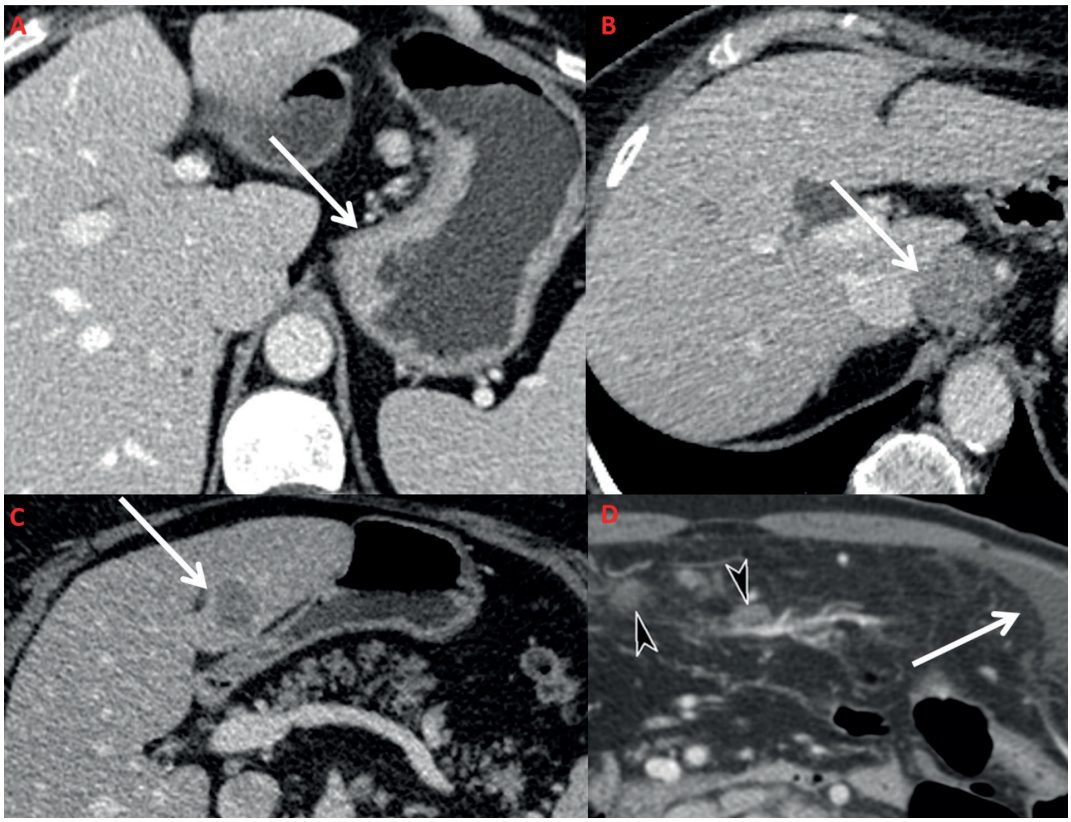

Figure 2. Gastric Cancer, Contrast Enhanced Computed Tomography (CECT). Axial **(A)** CECT image in the portal venous phase shows stomach distended by tap water with wall thickening of the small gastric curve (*white arrow*). Axial **(B, C)** CECT images in the portal venous phase report an enlarged enhanced perivisceral lymph node and a hypo-vascular liver metastases in the left lobe (*white arrows*). Axial **(D)** CECT image in the late phase demonstrates multiple peritoneal implants (*black arrowhead*) and ascites in the left side (*white arrows*).

sions. The monocromatic beam with DECT also helps in differentiating between fibrosis and true disease for serosa implants[105-110].

Public concern about radiation exposure has recently increased due to the rapid growth of CT use in medical applications. However, there are no established radiation dose limits for patients undergoing radiographic imaging, and risk-benefit evaluations should be performed to establish such guidelines. A long-term retrospective cohort study[105] demonstrated that patients with histories of malignancy or active malignancies experienced much higher radiation exposure than patients without malignancies. Considering that about 14.9-19.5% of gastric cancer patients are younger than 45 years of age, with a 5-year overall survival rate of about 70%, and rates that reach 90% in stage I and II cases, there are growing concerns regarding cumulative radiation exposure due to lifelong radiologic surveillance. Therefore, it is necessary to estimate the current state of radiation exposure due to repeated follow-up CT imaging in gastric cancer patients for the risk-benefit analysis of postoperative follow-up imaging[109]. When performing CT scans, conventional wisdom was that a patient's exposure to radiation is justifiable when the individual benefit outweighs the risk posed by radiation. Today, most doctors perform regular post-operative follow-up due to legal issues for themselves and their patients and because locally recurrent cancers or secondary gastric cancer after a gastrectomy can be cured by surgical resection in up 80% of cases with early diagnosis[109]. However, there is a lack of evidence that postoperative imaging follow-up extends patient survival, and therefore, the risks of cumulative radiation exposure must be considered in balance with the anticipated benefits of recurrent imaging at the level of the individual patient[109]. Unlike CT, ultrasound or MR imaging does not generate ionizing radiation. Since contrast-enhanced ultrasound and MR have limited diagnostic performance to detect peritoneal or deep-seat and lymph node recurrence, ultrasound and liver MR are not used for post-operative follow-up. However, in a limited set of patients with TNM stage I or early cancer (EGC), ultrasound and MR could be used as alternative follow-up imaging modalities combined with CT, especially 2-3 years after surgery[109]. In addition, several studies[110-112] indicated how MRI has a remarkable performance in preoperative staging, treatment response evaluation, predicting prognosis and histopathological features, treatment guidance and molecular imaging, but its use is restricted as it is limited to the abdominal cavity. Joo et al[110] reported how MRI has similar high performance in metastasis detection compared to CECT, showing an accuracy of 95.9%, and can be used as a problem-solving tool in the assessment of suspected liver localization identified at CECT. Giganti et al[111] reported how the evaluation of DWI has been recently showed as a promising biomarker of survival. Apparent Diffusion Coefficient (ADC) values of GC were lower in patients with poor prognosis. ADC value < 1360×10^{-6} mm^2/s is significantly correlated to lower overall survival[111]. In addition, several scholars prognosis[111-114]. reported how GC perfusion, assessed with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), is related to

Colon Cancer

Colon cancer (CC) represents an important socio-health problem with more than 1.4 million new cases a year worldwide. In Western countries, it represents the second malignant tumor by incidence after that of the breast in women and the third after that of the lung and prostate in men. It affects men more than women usually aged between 60 and 75 years[115]. The last decade has seen an increase in the diagnosis of colorectal cancer with a simultaneous decrease in the mortality rate thanks to the application of accurate screening programs, early diagnosis and the development and improvement of increasingly personalized therapies. CT has become a pivotal investigation in the study of colon cancer playing a fundamental role in screening, diagnosis and follow-up[116]. In this scenario, the latest ESGE (European Society of Gastrointestinal Endoscopy)/ESGAR (European Society of Gastrointestinal and Abdominal Radiology) 2020 guidelines put the CT colonoscopy or coloCT (CTC) in a central role in screening strategies. It has been identified as the radiological examination of choice for the diagnosis of colon cancer. Moreover, a central role has been attributed to CTC in patients with incomplete optical colonoscopy, as already highlighted by many papers in literature[116]. However, coloCT is not recommended as a primary test for population screening by ESGAR and ESGE, mainly due to the lack of solid evidence on its cost-effectiveness. The European guidelines in colorectal cancer screening, which recommend

immunohistochemical examination on feces for organized screening of CRC, suggest considering coloCT as a new screening technology under evaluation and evolution[117].

CTC studies should be performed using a low-dose, non-contrast CT technique on a multidetector CT scanner and in such a way that there is adequate adaptation of CTDIvol to the size of the patient, using an automatic exposure control. The recommended radiation output for routine screening coloCT should be less than or equal to half the diagnostic reference level for routine pelvic abdominal CT. In the context of screening programs, the reason for patients' greater adherence to CTC rather than colonoscopy lies in the three most common deterrents expressed by patients regarding undergoing a colonoscopy: bowel preparation, embarrassment, and fear of discomfort[118]. The advantage of coloCT is the use of a more-gentle preparation or an unprepared exam (without laxatives). In addition, pain related to colon distension by air can be minimized through the use of carbon dioxide delivered by an electronic injection pump. The use of carbon dioxide is also associated with faster absorption, making the patient more comfortable immediately after the examination[119].

Another fact in favor of coloCT (Figure 3) is that, unlike colonoscopy, it can detect extracolonic anomalies, although with limitations when low-dose protocols are used[120]. The great limitation of the sensitivity of the CTC is represented by its closely link to the experience of the performing radiologist, with high detection rates and positive predictive values for radiologists who have reported more than 1000 coloCTs in total with more than 175 cases per year[121]. In addition, the coloCT presents two major problems in terms of safety: the risk of perforation, a rare event (0.04% of cases), and the patient's exposure to ionizing radiation. An international study[122] found that the mean effective dose for a screening coloCT is

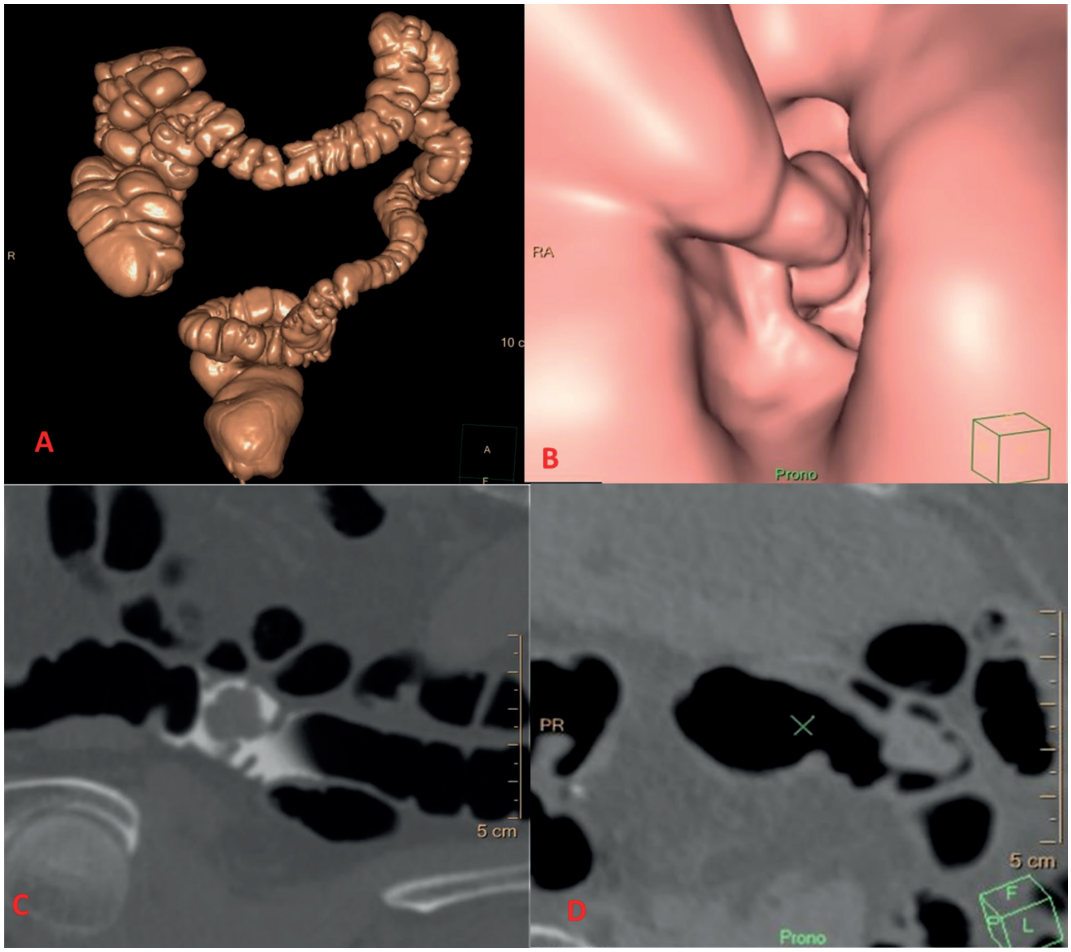

Figure 3. CT COLONOSCOPY: this imaging technique allows to obtain images of the colon in Volume Rendering **(A)**, virtual endoscopy **(B)** and multiplanar **(C-D)** reconstructions essential for the study of polyps.

4.4mSv using low dose scanning protocols. Even lower doses can be achieved using iterative reconstructions. In this regard, a Japanese study[123] observed how low dose coloCT with iterative reconstruction reduces the radiation dose from 48.5 to 75.1% without image quality degradation compared to routine dose coloCT with filtered rear projection and with a substantially overlapping sensitivity rate in identifying polyps > 10 mm[124]. We also need to consider, in a screening scenario, that coloCT should be repeated every 5 years, not earlier. For a radiation dose of about 4-6 mSv at age 50, the lifetime risk of cancer death varies between 0.02% and 0.03%[124]. Although the cancer risk of such small doses of ionizing radiation is still debated, the models suggest that the number of radiation-induced cancers will be significantly lower than the number of colon cancer prevented by screening[125].

After the diagnosis, an accurate and careful staging of the CC in the preoperative phase is necessary to determine operability based on tumor growth on adjacent structures and the presence of distant metastases as well as to identify any complications that may affect patient management (perforation, abscess, or pulmonary embolism). With radiomics it is also possible to detect information regarding the instability of microsatellites, a prognostic factor for the CC and also important for setting specific therapies[126].

CT plays a primary role for the information about local involvement: tumor dimensions (thickness and length), circumferential involvement, and invasion of pericolic fat, invasion or thickening linear or nodular of the visceral serosa in contact with the tumor, invasion of the abdominal or pelvic muscles, and lymph node involvement. CT demonstrates high sensitivity in demonstrating lesions that infiltrate and exceed the colonic wall (T3-T4) (Figure 4), also allowing to highlight complications, such as obstruction, perforation and fistulas[127]. Lymph node involvement is important in the preoperative staging phase and for the treatment and it is an independent prognostic predictor. The main factor of interest in clinical practice is size (> 10 mm), with high specificity and negative predictive value, respectively 80.9% and 80.2%. Additional aspects, such as contrast characteristics, internal inhomogeneity, rounded shape or short axis/long axis ratio > 0.7 are parameters to be considered in this evaluation[128]. Uneven and circumferential contrast enhancement is a positive predictive factor for metastatic commitment, with a high specificity: on the contrary, an enhancement with benign characteristics is synonymous with benignity even with dimensions > 10 mm[129]. The role of CT is crucial in the study of metastasesM in this case it is appropriate to perform CT of brain/thorax/abdomen/pelvis with and without contrast medium. For subjects with known allergy to contrast medium, chest CT scan without contrast medium and brain/abdomen MRI with contrast medium (with possible premedication) will be used. Liver is the organ most affected by metastases. On CT, liver metastases appear as hypodense masses (calcified or cystic for the mucinous variant only) and are best visualized during the portal venous phase. The addition of the arterial phase would allow a better visualization of lesions less than 1 cm, which may have circumferential impregnation[130]. In lesions less than 1 cm, the sensitivity of CT is reduced while MRI with contrast medium is a more accurate examination[131]. The presence of synchronous lung metastases varies from 2-18% in colon cancer studies, representing the main secondary extra-abdominal localization[132]. Some authors[133] argue that the search for metastatic pathology of the chest by CT is not advantageous in the absence of liver metastases and colon cancer lymph nodes; other studies, on the other hand, argue that CT staging of the chest

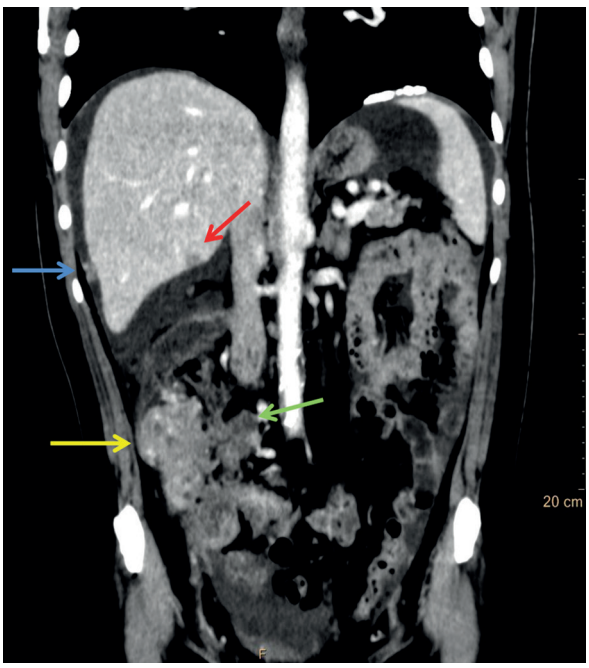

Figure 4. Voluminous right colon cancer (*yellow arrow*). It is possible to identify lymphnodal metastases (green arrow), ascites with peritoneal implant (*blue arrow*) an liver localization (*red arrow*)

is a standard exam to be performed in all patients with CC, as it can reveal significant metastases susceptible to curative surgical resection. There are currently no consistent guidelines regarding the use and effectiveness of the use of contrast medium for the search for lung metastases in patients with CCR. A recent study[134] evaluated the effectiveness of using contrast medium based on the stage of the tumor pathology. According to the results of the study, chest CT with contrast should be performed selectively and only in those patients whose tumor is beyond stage 0/I. This will reduce the number of unnecessary chest CT exams. However, even in early-stage patients, individual risk factors, such as old age and smoking must always be considered[134]. In addition to the lung and liver, colorectal cancer metastasizes into the peritoneum in a discreet proportion of case: about 15% of patients has synchronous metastasis, 4-19% will develop metachronous disease during follow-up[135]. Peritoneal carcinosis in CT appears as ascites, especially if lobulated, or alternatively as soft tissue nodules that adhere to the parietal peritoneum. These peritoneal implants usually enhance with intravenous contrast material and typically localize in pelvis, in the right colic flexure and in the greater omentum. In CT, the use of oral contrast material associated with intravenous contrast material allows assessment of smallest deposits[136]. When the involvement of the peritoneum is limited or small-sized, it may not be visible on CT; in this case, it should be assessed by MRI[137].

Currently, there is an involvement of CNS in 2% of cases and the main risk factors include k-ras mutations and the presence of pulmonary metastasis. In the majority of cases, patients are asymptomatic. Therefore, the occurrence of brain metastasis often results as an accidental event in staging with positron emission tomography (PET)-CT[138]. However, MRI is the most accurate diagnostic tool in brain metastases[139].

Currently, there is no standardized imaging protocol for follow-up phase, because has not been established the precise type of imaging to be done, the frequency and duration of the follow-up. About 80% of recurrences occur in the first three years, and 95% in the first five years. Therefore, the timing of the monitoring and the full duration of the follow-up were established based on these events[140]. ESMO guidelines recommend performing chest and abdomen CT every 6 to 12 months for the first three years in patients with the highest risk of recurrence. ASCO guidelines recommend performing abdomen and chest CT each year for three years in patients with highest risk of recurrence and when it is not possible a curative intent. An intensive follow-up, based on individual specific risk, has shown that it can increase overall survival, as well as the early diagnosis of asymptomatic relapse, susceptible to curative resection[141].

Pancreatic Cancer

In the past few decades, cross sectional imaging with CT and MRI have become irreplaceable in the assessment of patients with pancreatic tumors. CT is the standard for tumor detection and staging, thanks to its availability, high spatial resolution and rapid acquisition[142,143]. In the past, pancreas protocol CT was multiphase and included non-enhanced CT images, in order to identify calcifications or haemorrhage, and post-contrast acquisition with an early arterial phase (25-30 seconds), a late arterial/pancreatic phase (40-45 seconds) and a portal venous phase (70-80 seconds)[142,144]. With the use of bolus tracking, pancreatic CT protocols have become dual phase removing the early arterial in favour of the late arterial/pancreatic phase that shows excellent contrast enhancement of arterial structures, too[143]. Usually, 100-150 mL of iodinated contrast are injected at a rate of 3-5 mL/sec, and images are acquired with a thin slice of at least 2 mm for the pancreatic phase. The late arterial/pancreatic phase allows a good anatomic localization of the tumor, evaluating the extent of disease and the interface between tumor and arterial structures and identifying any vascular anomalous anatomy[144]. The portal venous phase is the more accurate to evaluate the tumors relationship to the superior mesenteric and portal vein and to identify hepatic metastases. Imbriaco et al[145] proposed a single-phase intermediate at 50 seconds after contrast administration to reduce radiation and concluded that it is effective for the pre-operative assessment of pancreatic tumors. Alternatively, only one post-contrast phase can be obtained with the split-bolus technique in which two boluses separated by a nearly 35 seconds interval are injected, so that in the same image there are the pancreatic and portal venous phase with consequent dose reduction[146]. While CT is the first line imaging of choice for pancreatic tumors, it still has some limits, like the radiation exposure. In addition, CT has a low accuracy in the detection and characterization of small pancreatic lesions and cystic lesions, given its lower contrast res-

olution[147,148]. At the same time, the CT sensitivity for liver metastases is only 70-75% and it is sub-optimal for lymph node metastases, too[149,150]. Finally, the response evaluation for local ablative therapies, used in patients with locally advanced pancreatic cancer, is a serious challenge with CT imaging because the dimensional criteria are not appropriate to assess these treatments[151]. Moreover, CT is not able to differentiate residual cancer from post-therapy inflammation and fibrosis in patients undergone neoadjuvant therapy[152,153]. However, the most recent CT technological advances, such as low-voltage acquisitions, DECT, perfusion CT, and the application of Radiomics and Artificial Intelligence, are promising techniques for the optimization of the protocol and for improving the CT diagnostic performances[154-157]. Low-voltage acquisitions with high performance X-ray tubes and iterative reconstructions improve contrast enhancement and tumor detection, with acceptable image quality, even if some limits remain in obese patients[147]. In addition, the low-dose acquisitions allow for reduction of radiation exposure for more than 25%[158]. DECT has many applications in pancreatic imaging. Similarly to low-voltage acquisitions, the production of energy-selective images, such as virtual monochromatic images at low keV (<65 keV), improves the contrast enhancement and lesion detection[159,160]. In pancreatic CT, the material-selective images, such as iodine maps or virtual unenhanced images have shown promising results. The iodine maps improve reader's confidence for lesion detection and differentiation. They are helpful in discrimination between solid and cystic lesions and between pancreatic tumors from mass-forming pancreatitis[161,162]. In addition, the quantitative evaluation of iodine maps could be a promising tool in the assessment of treatment response[163]. On the other hand, the virtual unenhanced images avoid the basal acquisition reducing radiation exposure of about 21%[164]. Perfusion CT studies follow the transit of an iodinated contrast agent, intravenously injected, from the intravascular into the extracellular space with multiple scans. This technique requires a small bolus of contrast material (12-18 g of iodine) with a medium-to-high concentration (> 300 mg/mL) injected at a high rate (≥ 4 mL/s). Two phases are acquired: the first requires a temporal resolution ≤ 2 s for 45 s, while for the interstitial phase a temporal resolution of 5-15 s is recommended according to the kinetic model applied for post-processing[147]. The quantitative parameters, extrapolated by the post-processing, can assess the microcirculation and pancreas perfusion. Therefore, perfusion CT parameters provide diagnostic and prognostic information in oncological diseases, such as pancreatic ductal adenocarcinoma (PDAC) and neuroendocrine tumors (NET). They are useful in differential diagnosis between PDAC and chronic, mass-forming pancreatitis[165]. In addition, perfusion CT is able to identify suitable patients to antiangiogenic therapy: usually, good responders to chemotherapy have higher values of blood flow and blood volume in PDAC while NET with lower replication index, benign behaviour, and no microvascular involvement show higher values of blood flow[166-168]. With the advent of Radiomics, it has been possible to extract from the radiological images relevant information for the diagnosis, management and prognosis of pancreatic neoplasms[169-172]. Cannelas et al[173] showed that radiomics features could be predictive of pancreatic NET grade and of disease progression after surgery. These results were confirmed by many authors, such as Benedetti et al[174] that assessed the ability of CT-derived radiomics features in discriminating histopathology of pancreatic NET. In their study, Chen et al[175] found that changes in CT radiomics features are helpful for early assessment of treatment response in patients with PDAC.

MRI is used frequently in pancreatic imaging as alternative tool or as an adjunct to CT in detection and characterization of lesions. It is considered a problem-solving tool thanks to its superior soft-tissue resolution in absence of radiation exposure[141]. Standard pancreatic MRI protocol includes T2 weighted coronal single-shot fast spin-echo (SSFSE), T2-weighted 2D axial fat-suppressed FSE, T1-weighted 2D axial in-phase and opposed-phase gradient echo (GE), axial echo planar diffusion-weighted imaging (DWI) with b values of 50, 500, and 1000, axial unenhanced and contrast-enhanced T1-weighted fat-saturated (arterial, portal, and delayed phases) and coronal contrast-enhanced T1 weighted with fat saturation (delayed phase 3-5 minutes after injection start). Coronal 2D and 3D single-shot MR cholangiopancreatography (MRCP) are recommended for cystic pancreatic lesions or in case of pancreatic duct or main bile duct involvement (figure 5)[176-179]. Despite the spatial resolution of MRI is lower than CT, gadolinium contrast enhancing T1-weighted sequence is able to assess vascular involvement of pancreatic cancer providing nearly equivalent information to contrast-enhanced

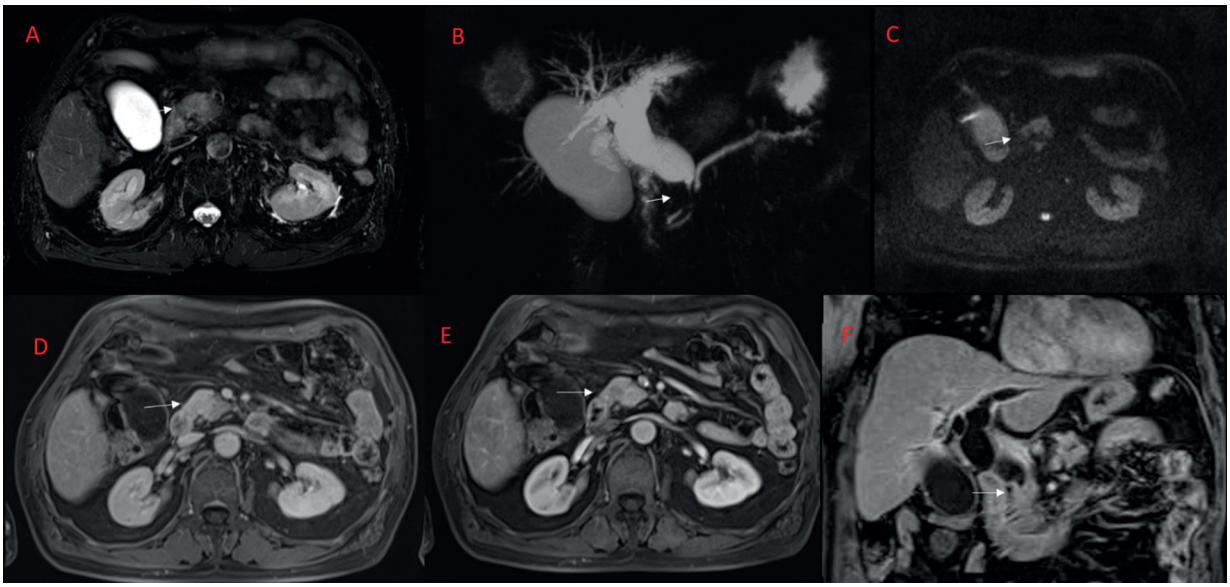

Figure 5. Head pancreatic adenocarcinoma. The lesion shows hyperintense signal on T2-W FS sequence **(A)**, with involvement of pancreatic duct (**B**: 3d colangiography sequence), restricted signal on DWI (**C**: b 800s/mm^2) and isointense signal on post contrast sequences (**D**: arterial phase; **E**: portal phase and **F**: equilibrium phase).

CT[180]. In addition, Motosugi et al[181] found that contrast-enhanced MRI had greater sensitivity in the detection of liver metastasis than CT. For patients with contraindications to contrast medium injection, non-contrast MRI protocol is indicated as alternative to CT[3]. DWI is particularly useful in those patients (Figure 6). Moreover, many studies[182-185] underlined how DWI is helpful to detect small pancreatic NETs and metastasis. Therefore, Verde et al[186] proposed an abbreviated MRI protocol for detection and surveillance of pancreatic NETs in patients with multiple endocrine neoplasia type 1 (MEN-1). They found that DWI and T2-weighted images had the highest diagnostic performance in detecting PNETs, suggesting an abbreviated MRI protocol without contrast medium administration in MEN-1 patients undergoing imaging follow-up[186]. For the screening of pancreatic cancer in patients with BReast CAncer susceptibility gene (BRCA) mutation, Corrias et al[187] proposed an abbreviated pancreatic MRI protocol performed in conjunction with breast MRI. They suggested a rapid screening pancreatic MR protocol during less than 10 minutes and that consisted of: coronal navigator-triggered (NT) T2 SSFSE, axial NT T2 SSFSE, axial DWI (b=0, 20, 50, 80, 250, 500, and 800 s/mm2), and axial T1 post-contrast fast spoiled gradient echo (with contrast administration during the breast MRI examination)[187]. MRI with MRCP is recommended in the characterization and follow-up of cystic pancreatic lesions thanks to its superior contrast resolution without exposure to ionizing radiation[188]. For the surveillance of cystic disease, abbreviated MRI protocols represent a good alternative. In literature, it has been suggested an MRI protocol without administration of a contrast agent. In their retrospective study on 56 patients with pancreatic cysts, Macari et al[189] found that contrast-enhanced images did not lead to different treatment recommendations compared to unenhanced images[189]. Nougaret et al[190] found similar results with their follow-up in 301 patients and 1174 cysts: they reported that the only predictor of malignancy is the size of the cyst at diagnosis and the MRI protocol with administration of contrast agent did not provide any additional information[190]. Pedrosa et al[191] suggested to reserve the standard contrast-enhanced MRI protocol with MRCP for the initial evaluation of pancreatic cystic lesions while for the follow-up they proposed a 10-min MRI protocol consisting of the following sequences: axial and coronal SSFSE T2-weighted, 2D and 3D singleshot MRCP, and 3D T1-weighted spoiled gradientech[191]. On the utility of DWI in the surveillance of pancreatic cystic lesions, there is a debate in literature. Pozzi-Mucelli et al[192] in their retrospective study on 154 patients with pancreatic cystic neoplasms, concluded that a short protocol MRI with T2-weighted and unenhanced 3D T1-weighted (total examination time 7-8 min) is

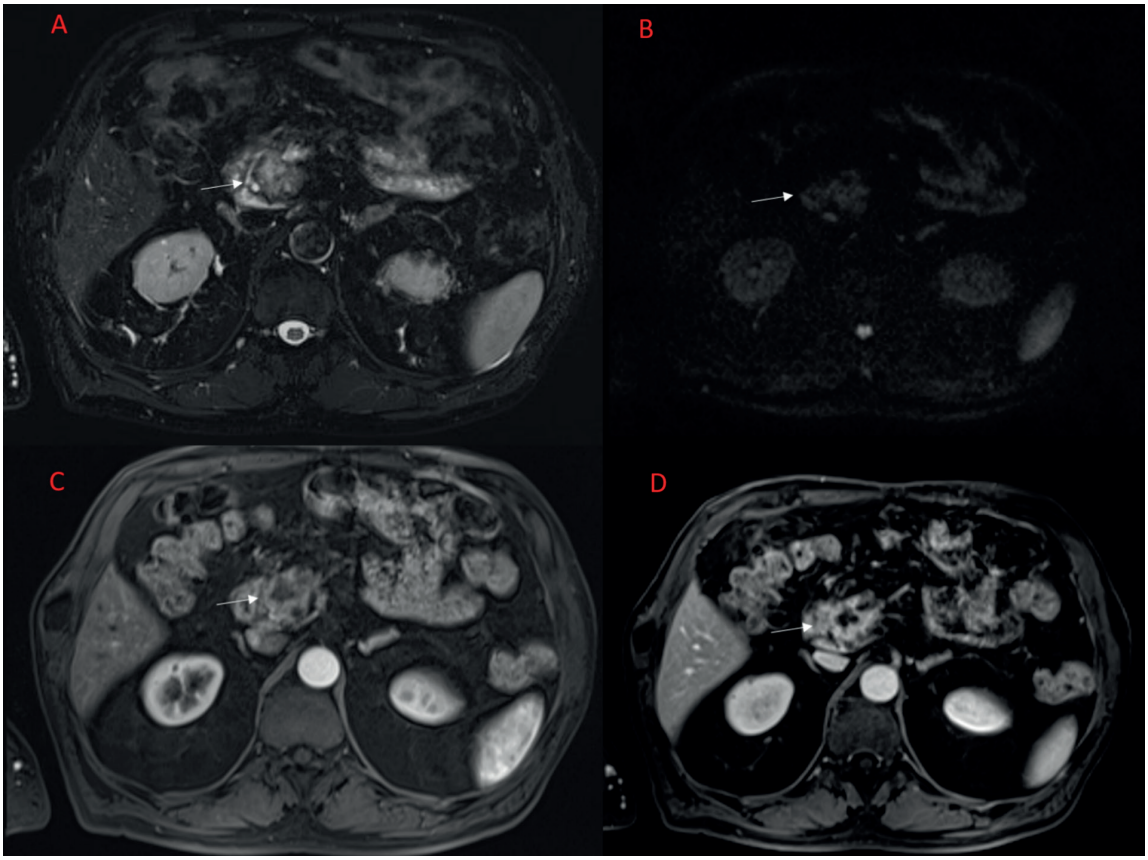

Figure 6. Head pancreatic adenocarcinoma. The lesion shows hyperintense signal on T2-W FS sequence **(A)**, restricted signal on DWI (**B**: b 800s/mm^2) and hypointense signal on post contrast sequences (**C**: arterial phase; **D**: portal phase).

more economical and provides equivalent clinical information for patient surveillance compared to a comprehensive-protocol.

Furthermore, DWI provides functional data that, as well as quantitative parameters of DCE-MRI, have an important role in predicting tumor biology and grading and in the assessment of treatment response[193,194]. Granata et al[195] found that DWI-derived perfusion-related factors might be helpful to differentiate pancreatic tumors and peritumoral inflammatory.

Texture analysis (TA) is a form of radiomics that refers to quantitative measurements of the histogram, distribution and/or relationship of image pixels signal intensity. MR-TA has multiple limitations: many texture data are sensitive to multiparametric acquisition and reconstruction data (flip angle, repetition time, echo time, field-of-view, contrast, slice-thickness, and reconstruction algorithms affect pixels intensity, spatial relationships, and edges)[196-199]. To minimize these effects, image protocol standardization and the use of image filtration methods have been utilized. Another major challenge with MR-TA is the volume produced data: with many texture tools generating hundreds or thousands of measurements. Moreover, it is difficult to understand the texture parameters meaning, and it is complicated to identify relationships between one or more texture features and a biologic outcome when the number of texture parameters exceeds the patient sample size. Quantitative MR-TA has been evaluated in a limited manner in PDAC. A retrospective study[200], including 66 patients with pancreatic cancer, found that tumor size and MR-TA data were predictive of both recurrence-free survival and overall survival in univariate analysis. In contrast, only tumor size remained predictive in multivariate analysis[201].

Conclusions

The increase in knowledge in oncology and the possibility of creating personalized medicine by selecting a more appropriate therapy related

to the different tumor subtypes, as well as the management of patients with cancer within a multidisciplinary team, has improved the clinical outcomes. Early detection of cancer through screening based on imaging is probably the major contributor to a reduction in mortality for certain cancers. Nowadays, imaging can also characterize several lesions and predict their histopathological features and can predict tumor behaviour and prognosis. CT is the main diagnostic tool in oncologic imaging and is widely used for the detection, staging and follow-up of tumors and since CT accounts for 49-66% of overall patient radiation exposure, the constant reduction, optimization as well as inter- and intraindividual consistency of dose are major goals in radiological field.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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