1 - Gastrointestinal stromal tumours are rare mesenchymal neoplasms originating from the Cajal cells and represent the most common sarcomas in the gastroenteric tract. Symptoms may be absent or non-specific, ranging from fatigue and weight loss to acute abdomen. Nowadays endoscopy, echoendoscopy, contrast-enhanced computed tomography, magnetic resonance imaging and positron emission tomography are the main methods for diagnosis.

2 - Gastrointestinal stromal tumours may not be included immediately in the differential diagnosis of a solitary abdominal mass. Radiomics is an emerging technique that can extract medical imaging information, not visible to the human eye, transforming it into quantitative data. The purpose of this review is to demonstrate how radiomics can improve the already known imaging techniques by providing useful tools for the diagnosis, treatment, and prognosis of these tumours.

3 - Gastrointestinal stromal tumours (GISTs) represent the most common sarcomas in the gastrointestinal tract. They were first recognized by Mazur and Clark in 1983 as a unique variety of "stromal tumour" and in 1998, Kindblom et al. demonstrated their morphological and immunophenotypic characteristics similar to the interstitial cells of Cajal, the pacemaker cells of gastrointestinal movement.

4 - GISTs' annual incidence is about 1.5/100,000, slightly higher in males with a median age of approximately 60–65 years. The most frequent onset sites are stomach (50%), small bowel (25%), rectum (5%), oesophagus (< 5%), duodenum (< 5%) and other locations (< 5%). In this case, GISTs are termed extraintestinal GISTs (E-GISTs) and are localised in the omentum, mesentery,retroperitoneum, or pleura, showing behaviour similar to gastrointestinal forms.

5 - Patients with GISTs can be asymptomatic or experience non-specific symptoms including early satiety, fatigue, abdominal pain, fever, and weight loss. However, when tumour size becomes significant, the clinical presentation may be an acute abdomen due to tumour rupture, gastrointestinal obstruction, or appendicitis-like pain.

6 - Most GISTs are driven by activating mutations in KIT (75%) or PDGFRA (10%) genes, that are responsible for the up-regulation of crucial signalling pathways including MAPK and PI3K-AKT; GISTs lacking in one of these two mutations are called 'wild type' (wt-GISTs) The malignant potential of GISTs greatly varies from benign tumours to rapidly progressing cancers; approximately 30% of GISTs are malignant and histopathological analysis is crucial to predict the risk of local recurrence or distant metastases.

7 - The most commonly used prognostic classification stratifies patients into very low-risk, low-risk, moderate-risk and high-risk groups according to mitotic index, tumour site and tumour siz. Complete surgical excision is the first choice therapy in case of localised tumours, whereas lymphadenectomy is not usually necessary due to the rare lymph node involvement.

8 - Medical therapy mainly employs Imatinib, a selective tyrosine kinase inhibitor usually used when the tumour is clinically advanced, metastatic or unresectable. Imatinib therapy is also important as neoadjuvant treatment in

locally advanced forms and in the postoperative phase in order to reduce the risk of recurrence in high-risk GISTs. Other biologic treatments are Sunitinib (second-line tyrosine kinase inhibitor) and Regorafenib (third-line multikinase inhibitor).

9 - Mutational analysis can be useful as a prognostic marker and as a predictive tool for response to molecular-target therapy; in particular, wt-GISTs are usually unresponsive to the kinase inhibitor therapies. To determine the appropriate therapy, an accurate diagnosis is essential. Even though endoscopy, echoendoscopy, magnetic resonance imaging (MRI) and positron emission tomography (PET) can be useful for the detection of GISTs, the first choice imaging examination for diagnosis and follow-up is contrast-enhanced computed tomography (CECT).

10 - The high subjectivity of the CECT, the lack of validation and the growing need for accurate and objective risk stratification have led to the introduction of quantitative techniques such as radiomics. The purpose of this review is to conduct a literature review on the application of this growing technique that can help the more or less experienced radiologist with the diagnosis and follow-up of GISTs.

11 - Radiological diagnosis of GISTs is similar to that of other cancers developed in the gastrointestinal tract, although imaging features may vary depending on the size and aggressiveness of the tumour. Ultrasonography (US) is a rapid and radiation-free imaging technique, nevertheless it is not always useful for the study of the digestive tract. When GIST is clinically advanced, ultrasound studies may reveal the primitive tumour as an abdominal hypoechogenic mass that can displace adjacent organs and vessels or the presence of hepatic metastases.

12 - Echoendoscopy may be the first imaging technique for tumour identification, parietal infiltration evaluation and sometimes for GISTs treatment. However, CECT and MRI have proven to be better methods for characterization of the lesion, the evaluation of its extension and the presence of possible pathological lymph nodes or distant metastases. Non Contrast-Enhanced CT (NCECT) may highlight possible endoluminal haemorrhage and calcification.

13 - Ileal location and irregular margins,, together with size larger than 10 cm, represent important negative prognostic factors. CECT is also important to study any distant metastases, frequently located in the liver or the peritoneum with a radiological appearance similar to that of the primary tumour. Moreover, CECT is the main imaging technique for assessing response to Imatinib therapy that can be seen as a rapid transition from a heterogeneously hyperattenuating pattern to a homogeneously hypoattenuating pattern with decrease in tumour vessels.

14 - The superior ability of MRI to difef rentiate between ful id, mucinous, or fibrous structures compared with CT may be useful in the study of tumour components of GISTs and in the evaluation of secondarisms in pelvic, hepatic, mesenteric, and peritoneal sites. Contrast enhanced MRI (CE-MRI) is proved to be useful in identifying hereditary paraganglioma pheochromocytoma syndrome (HPP) related tumours such as GIST when the unenhanced T2 weighted images highlight abnormal findings.

15 - Because of their characteristics, sometimes GISTs may not be included immediately in the differential diagnosis of a CT-detected solitary abdominal mass. In these cases the diagnosis is done by biopsy or surgery, exposing the patient to risks related to bleeding or tumour spread. This is why radiomics, an emerging method that can extract medical imaging information transforming it into quantitative data, is a particularly interesting field of research.

16 - Medical images reflect different pathophysiological properties of the body that can be converted into meaningful and extractable data not visible to the human eye through a quantifci ation process. The extraction of quantitative features and the selection of useful information for the characterization of normal and abnormal radiological images is the cornerstone of radiomics.

17 - Radiomics along with artificial intelligence, which has been proven to facilitate the work of the radiologist in its various subspecialties, can improve cancer and other pathologies diagnosis and treatment. Only a small part of radiologists continue to remain sceptical about their use. Literature is focusing on the oncological application of radiomics because of its ability to capture tissue and lesion properties such as shape and heterogeneity by images.

18 - Heterogeneity depends on factors such as cellularity, angiogenesis, extravascular matrix, and necrosis; a greater intratumoral heterogeneity corresponds to a poorer prognosis. In addition, studies have shown that some radiomic features are directly linked to genomic, transcriptomic, or proteomic characteristics and can give information on tumour aggressiveness and response to therapy. Furthermore, radiomics is a non-invasive method able to evaluate the entire pathological tissue adding new information for a personalised therapy.

19 - Current biopsies, instead, capture heterogeneity only within a small portion of tissue taken from a single anatomical site and that is not always feasible; this limits a proper assessment of the extent of phenotypic or genetic variation within a tumour . This method does not lead to automaticity in the diagnostic process, although it does add new quantitative data to existing data.

20 - The radiomics process is based on several steps, which are: image segmentation, feature extraction, feature selection, model establishment and evaluation. The first step is to select the region of interest (ROI) so that the information obtained relates only to the lesion under examination. This process can be done manually or with the use of automated segmentation algorithms and can lead to several two-dimensional or three-dimensional features.

21 - Radiomic feature classes can be divided into statistical based (including histogram-based and texture-based) model-based, transform-based, and shape-based. In particular, statistical-based techniques have been more commonly applied todescribe the relationship of grey level values in an image, compared with the model-based and transformed-based

methods. The statistical approach is able to extract texture parameters from the frequency of occurrence of different grey values.

22 - First-order features are based on a single-pixel or a single-voxel analysis and they provide useful generalised information about the global grey-level histogram including grey-level mean, medium and maximum intensity, standard deviation (SD), skewness (the asymmetry of the histogram) and kurtosis (flatness of the histogram). These features represent the clutter and complexity of the image, the amount of information and the more or less orderly distribution of pixels.

23 - First-order features are supplemented by second-order ones which are able to assess the inter-relationships between two pixels or voxels, they reflect space and distance, and fill the weakness of first-order statistical features. They include Grey-Level-Co-occurrence Matrix (GLCM), which embraces several features such as entropy, angular second moment (also called uniformity or energy), contrast and more.

24 - Furthermore, higher-order features are obtained by applying fliters (model based features) or mathematical transforms (transform based features) to images and give information on more than two pixels or voxels. Shape-based features are the simplest and describe geometric characteristics of ROI such as 2D and 3D diameters, axes, and their ratios. An example is sphericity, it consists of a ratio between two circles with the same surface area, one of which represents the tumour region.

25 - After all features of the ROI have been extrapolated, it is necessary to select those useful for our model to correlate these characteristics with diagnostic and prognostic data or biology. There are several methods of feature selection. The most commonly used is cluster analysis which consists in dividing the features into groups, called clusters, with internal similarities and low inter-cluster correlation, and selecting a single representative feature within each cluster.

26 - It becomes possible to use only features that are reliable and relevant to the study, avoiding overfitting. It would be appropriate to validate the chosen model with external data sets from difef rent centres and if no external data set is available, to proceed to the selected model assessment with an internal-cross validation by dividing the internal data into two or more subsets.

27 - Different radiomic models related to the molecular expression of Ki-67 in more or less rare tumours have been proposed. Low levels of Skewness and ClusterShade in the study of Cozzi et al. were indicators of aggressiveness as well as indicator of mediastinal lymph node metastasis in lung neuroendocrine tumours (NET). To carry out personalised therapy, radiomics can quantify receptor expressions (i.e. PDL1; EGFR) or mutations.

28 - In the Agazzi et al. study first-order features, including skewness, showed high values in EGFR-mutated adenocarcinomas while ALK-arranged tumours had the lowest values. Consistently Bracci et al. Demonstrated that Skewness was low in tumours with PD-L1 expression ≥ 1% and ≥ 50%, thus in worse prognosis tumours. Other low features values related with higher receptor expression were Sphericity, LGZE and GLNU. These last two represent the distribution of low grey-level areas in three-dimensional (3D) space and nonuniformity of grey level areas, respectivel.

29 - More malignant lesions, therefore, would appear less spherical and with a more uniform microstructure than more benign lesions with PD-L1 < 1%. It has been repeatedly demonstrated the effectiveness of radiomics in assisting diagnosis and defining malignancy of rare tumours such as neuroendocrine neoplasms (NEN).

30 - Tumour volume and several NCECT and CECT radiomic features (voxel alignment, neighbourhood intensity-difference and intensity-size-zone families) were able to identify microscopic vascular infiltration. Chiti et al. used radiomic analysis to predict pathologic grade in patients with gastroenteropancreatic-NEN (GEP-NEN). They found that shape and I order features were able to distinguish between low and high grade GEP-NEN both in arterial and venous CECT.

31 - Radiomics features obtained in the pre- and post-treatment examination of histopathologically different lesions allow a prediction of response to therapy, progression free survival (PFS) and overall survival (OS). A practical example is the response to radio-chemotherapy in patients with locally advanced rectal cancer. Cusumano et al. identifei d how the maximum fractal dimension (a model based features), energy and GLNU were able to define a radiomic model for the prediction of complete pathological response.

32 - Gregucci et al. found that the GLCM and Neighbour Intensity Difference (a NGTDM feature) are both independent predictor variables for local response in locally advanced pancreatic cancer treated with stereotactic body radiotherapy, although it was not possible to create a validation cohort due to the small sample size. Han et al. study showed that a clinical model enriched with radiomic features was more predictive than a purely clinical model in assessing the OS of patients with clear cell carcinoma after nephrectomy.

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