A Systematic Review on the Role of the Perfusion Computed Tomography in Abdominal Cancer

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Abstract

Background and purpose: Perfusion Computed Tomography (CTp) is an imaging technique which allows quantitative and qualitative evaluation of tissue perfusion through dynamic CT acquisitions. Since CTp is still considered a research tool in the field of abdominal imaging, the aim of this work is to provide a systematic summary of the current literature on CTp in the abdominal region to clarify the role of this technique for abdominal cancer applications.

Materials and Methods: A systematic literature search of PubMed, Web of Science, and Scopus was performed to identify original articles involving the use of CTp for clinical applications in abdominal cancer since 2011. Studies were included if they reported original data on CTp and investigated the clinical applications of CTp in abdominal cancer.

Results: Fifty-seven studies were finally included in the study. Most of the included articles (33/57) dealt with CTp at the level of the liver, while a low number of studies investigated CTp for oncologic diseases involving UGI tract (8/57), pancreas (8/57), kidneys (3/57), and colon–rectum (5/57).

Conclusions: Our study revealed that CTp could be a valuable functional imaging tool in the field of abdominal oncology, particularly as a biomarker for monitoring the response to anti-tumoral treatment.

Keywords
computed tomography perfusion, abdominal imaging, perfusion parameter, abdominal cancer

Introduction

Perfusion Computed Tomography (CTp) is a minimally invasive technique which allows quantitative and qualitative evaluation of tissue perfusion by injecting an iodinated contrast agent and performing dynamic CT acquisitions to estimate time enhancement curves within organs and tissues.1,2 Physiological parameters, such as flow rate or local blood volume, can subsequently be calculated from the time enhancement curves by means of mathematical perfusion models. From a technical standpoint, CTp is the result of the development of new multi-slice CT systems and post-processing software and consists in a rapid serial images acquisition after bolus injection of a high flow (4–10 mL/s) iodinated contrast with a low contrast media volume (generally 40 to 50 mL).3 The contrast injection with a high iodine concentration allows to increase the enhancement of the examined tissues. Then, by means of post-processing software, it is possible to obtain attenuation curves based on kinetic models and perfusion algorithms which vary depending on the organ investigated. Time attenuation curves are then analyzed to quantify color maps that represent the functional state of the vascular system such as blood flow (BF), blood volume (BV),

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and contrast transit measurements such as mean transit time (MTT) and time to peak (TTP). Among the innovations that lead to the CTp development, there are the increase in the number of detectors, which allows to investigate larger body areas and reduce the thickness of the individual slices, improving the spatial resolution of the CT and consequently the image quality and information obtained. Moreover, the increase in the rotation frequency of the X-ray tube-detector complex improved the temporal resolution of the CT and reduced the duration of the scan, thus allowing to perform the breath examination suspended and reduce breath artifacts thanks also to the introduction of new filters for the noise attenuation and the use of special software for correction of patient movements. Finally, with the development of new image processing software, it is possible to calculate perfusion parameters with the creation of color maps relating to each pixel of tissue analyzed. Based on these technical evolutions, CTp has been well established in the study of brain perfusion and has turned out to be the modality of choice for applications in this field. In particular, CTp is largely used to assess acute stroke, as well as to explore the tissue viability highlighting the changes in the mechanisms of self-regulation following an acute ischemia. In the field of oncology, there has been an increasing interest in the use of CTp, with a wide range of clinical applications, including lesion detection and characterization, identification of metastases, prediction of prognostic information based on tumor vascularity, and prediction and assessment of response to chemoradiation treatments and antiangiogenic drugs.

In the field of abdominal imaging, CTp is still considered a research tool. This is mainly because it requires the acquisition of multiple samples of the same anatomical region with relatively high temporal resolution, and this is generally associated with relatively high radiation exposure. Furthermore, results of CTp studies depend on the choice of acquisition parameters, mathematical perfusion model, software implementation, and the anatomical region. However, the increasing availability and simplicity of CTp, together with its ability in quantification of the abnormal vasculature within tumors (thus allowing the assessment of tumor aggressiveness) led to a growing interest in CT imaging method to examine several oncologic diseases associated with abdominal organs. In particular, the ability of CTp to study microvascular changes in angiogenesis reflecting tumor perfusion in vivo could be of particular interest for investigating liver and pancreatic lesions. In the management of hepatocarcinoma (HCC), CTp is considered a safe and specific imaging tool for diagnosis, choosing a therapeutic procedure, and evaluating response to therapy by showing changes in various perfusion parameters such as BV and TTP. Moreover, in case of liver metastases, CTp allows the visualization of occult lesions in comparison to other imaging methods, thanks to the hemodynamic changes highlighted by an increase in the enhancement of the liver parenchyma during CT acquisition and resulted useful for survival prediction and response to treatment. CTp was also able to assess changes in liver cancer perfusion in response to a specific anticancer therapy. CTp can help in the evaluation of malignant pancreatic tumors. In fact, it was observed that extrapolated values from CTp, such as BF and BV, provided optimal sensitivity and specificity to differentiate pancreatic adenocarcinoma from mass-forming chronic pancreatitis. Other studies have shown promising results concerning the role of CTp for colorectal cancer applications, such as diagnosis, angiogenesis evaluation, and pre-operative pathological grading. The role of CTp was also investigated for diagnosis of kidney carcinoma.

Based on these results, and thanks to the development of advanced equipment and the availability of commercial software platforms, CTp may provide a solid basis for obtaining additional functional imaging information, as an integral part of a conventional CT exam that could change the diagnostic and therapeutic process of patients with tumors involving abdominal district tumors. However, the still present drawbacks, mainly related with the lacking consensus on which CT protocol to use and the fact that published literature is based on small studies with different perfusion algorithms, have resulted in the missing integration of CTp into routine clinical practice protocols for abdominal imaging. In this context, we performed a systematic literature review on the application of CTp in abdominal cancer to provide a systematic overview of the application of CTp in abdominal cancer and clarify the role of this technique for abdominal imaging in clinical practice.

Materials and Methods

Search Strategy and Selection Criteria

A systematic literature research was performed to identify all original articles investigating the role of CTp for oncological applications in the abdominal district. The most relevant scientific electronic databases (PubMed, Web of Science, and Scopus) were explored and used to build the literature search. Studies published from 2011 to April 2021 were selected. The search strategy included keywords listed in Supplementary Materials-S1 section. The literature search was limited to English language publications and studies on human subjects. Two reviewers, after having independently screened identified titles and abstracts, assessed the full text of articles that evaluated the use of CTp in the abdominal district and that were original articles (not review articles, case studies). For articles meeting these criteria with full text available, the following further selection criteria had to be fulfilled: involvement of adult patients (age > 18); missing information on the CTp parameters investigated.

Data Extraction and Study Planning

After selection procedure, the following data were extrapolated from selected articles and collected in a table: author names; publication year; study type (retrospective and/or prospective); clinical purpose (diagnosis, grading, prognosis, response to treatment); sample number; info on study group analyzed in the study; anatomic district of interest; perfusion acquisition details;
information on placement of regions of interest (ROIs), namely the segmentation method (manual, semi-automatic, automatic) and the ROI type (2D or 3D); main results; and conclusions. The articles were classified and analyzed according to the abdominal area investigated in the study.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement29 (See Supplementary Materials-S2 section-for PRISMA Checklist).

Quality Assessment

The quality of the included studies was assessed through the QUADAS-2 tool for diagnostic studies and the QUIPS tool for prognostic studies. Two reviewers independently assessed the quality of each study, and any disagreements were resolved by consensus. For the QUADAS-2 tool, four domains were evaluated: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. At each domain, the quality of the elements was classified as “low,” “high,” or “unclear.”30 For QUIPS, six domains were evaluated: (1) study participant selection, (2) study dropout, (3) prognostic factor measurement, (4) outcome measurement, (5) study confusion, and (6) statistical analysis and reporting. The bias risk assessment was obtained using the answers “yes,” “partial,” “no,” or “don’t know” for 3 to 7 elements within each domain and were combined to assign an overall rating for each domain as “high,” “moderate,” or “low” risk of bias.31,32

Results

Study Selection

A total of 544 articles were retrieved from the PubMed, Web of Science, and Scopus databases. Following the removal of 72 duplicate articles, was performed a screening based on titles and abstracts of the remaining 472 articles. 364 records in this step were excluded for the following reasons: 100 were case reports and 264 were off-topic/review articles. The screening by titles and abstracts produced 108 articles, potentially usable for the systematic review description, of which the full text was evaluated. Of these articles, 17 records were excluded because they were not in English and 34 articles were off-topic and/or review articles. Among articles that were out of topic, 4 studies were excluded because they had a methodological purpose, while 3 were excluded because they aimed at investigated repeatability and reproducibility of CTp parameters. Finally, 57 records were included for the qualitative synthesis. The PRISMA flowchart of studies included according to the inclusion and exclusion criteria was reported in Figure 1.

Characteristics of Included Studies

Characteristics of the 57 selected articles are summarized in Table 1. The median number of individuals (range) was 37 (7-126). Study designs were 68.4% (39/57) prospective
Table 1. Characteristics of Included Studies. R = retrospective; P = prospective; FOV = field of view; M = manual; S = semi-automatic; A = automatic; mVI = microvascular invasion; MVD = microvessel density; HCC = Hepatocellular carcinoma; PDAC = pancreatic ductal adenocarcinoma; mNET = neuroendocrine tumor; PanNETs = pancreatic neuroendocrine tumors; AP = acute pancreatitis; CP = chronic pancreatitis; AML = angiomylipoma; NASH = Non-Alcoholic SteatoHepatitis; CRC = colorectal cancer; pRCC = papillary renal cell carcinoma; ccRCC = clear cell RCC; CRLM = colorectal cancer liver metastases; CCRT = concurrent chemoradiotherapy; GEJ = gastroesophageal junction; GIST = Gastrointestinal stromal tumor; AGC = Advanced Gastric Cancer; LAGC = locally advanced gastric cancer; RFA = radiofrequency ablation; IL-8 = interleukin 8; FU1 = after TACE; FU2 = follow-up; TACE = transarterial chemoembolization; TARE = transarterial radioembolization; TACLI = transarterial chemo-lipiodol infusion; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; SBRT = Stereotactic body radiotherapy; T2 = transition zone; C2 = central zone; P2 = surrounding parenchymal zone; DEB-TACE = doxorubicin-eluted bead-TACE; AUC = area under the curve; MFCP = mass-forming chronic pancreatitis.

| Author            | Year | Study type | Aim                                                                 | Patients | Zone                      | Acquisition details                                                                 | ROI Info                  | CTP parameters                  | Results                                                                 | Conclusion                                                                 |
|-------------------|------|------------|----------------------------------------------------------------------|----------|--------------------------|--------------------------------------------------------------------------------------|----------------------------|-----------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Delrue et al      | 2011 | R          | Compare perfusion parameters in different pancreatic diseases with a control population | 54       | Pancreas Tube voltage: 100 kVp; tube current-time product: 145 mA; slice thickness: 5 mm; FOV: 376 mm; total duration of acquisition: 51 s | M 2D ROI, BV, BF and PS | BF and BV are significantly lower in AP and CP compared to the control group. In adenocarcinoma tumors, BF and BV are lower but gradually increasing toward the tumor rim. | Compared to the control population, significant decreases in perfusion values were observed in all pancreatic pathologies under study, except in neuroendocrine tumors. | CTP allows non-invasive assessment of vascularization in the tumor tissue. |
| Delrue et al      | 2011 | R          | Evaluate CTP characteristics in the normal pancreas and in patients with pancreatic adenocarcinoma | 40       | Pancreas Tube voltage: 100 kVp; tube current-time product: 145 mA; slice thickness: 5 mm; FOV: 376 mm; total duration of acquisition: 51 s | M 2D ROI, BV, BF and PS | BF and BV in pancreatic adenocarcinoma were lower than in controls. PS is higher in tumor tissue. Perfusion values gradually increased toward the tumor rim. | Compared with the normal pancreas, a 60% reduction in BF and BV was observed in the tumor tissue. Perfusion values gradually increased toward the tumor rim. | CTP can provide additional quantitative hemodynamic information of pancreatic adenocarcinoma and mass-forming CP. |
| Lu et al          | 2011 | R          | Investigate CTP in patients with pancreatic cancer and mass-forming CP | 112      | Pancreas Tube voltage: 100 kVp; tube current-time product: 145 mA; slice thickness: 5 mm; FOV: 376 mm; total duration of acquisition: 50 s | M 2D ROI, BV, BF, TTP, PEI, PS | BF and BV in patients with pancreatic adenocarcinoma and mass-forming CP were lower than in controls. PS is higher in tumor tissue. Perfusion values gradually increased toward the tumor rim. | BF and BV in patients with progressive disease with cut-off values for BF and BV predicting progressive disease in 83.3%, 77.8%. | CTP allows non-invasive assessment of vascularization in the tumor tissue. |
| Petralia et al    | 2011 | P          | Evaluate the role of CTP for monitoring and predicting therapy response in patients with HCC treated with thalidomide | 24       | Liver Tube voltage: 100 kVp; tube current: 260 mA; perfusion scan delay: 9 s | M 2D ROI, BV, BF, PEI, TTP, PS | In the extrahepatic and intrahepatic lesions good responders show significant lower perfusion values than poor responders. | Baseline BF and BV predict response to therapy. | Characteristic perfusion patterns of metastatic GIST lesions show a good or poor response to molecular pharmacotherapy. |
| Schleimer et al   | 2011 | R          | Evaluation of CTP patterns in metastatic GIST lesions with sunitinib or imatinib in responders and non-responders | 46       | UGI Tube voltage: 100 kVp; tube current: 80 mA; slice thickness: 4 mm × 7.2 mm; perfusion scan time: 6 s/10 s | M 2D ROI, BV, BF, PEI, TTP, PS | Baseline BF and MTT may discriminate responders from non-responders. BF, BV and PS are not significantly different in responders and non-responders. | Characteristic perfusion patterns of metastatic GIST lesions show a good or poor response to molecular pharmacotherapy. | Baseline BF and MTT may discriminate responders from non-responders to chemotherapy. |
| Yao et al         | 2011 | P          | Evaluate the relationship between CTP and gastric tumor angiogenesis | 37       | Colon Tube voltage: 120 kV; tube current-time product: 100 mA; matrix: 512 x 512; perfusion scan delay: 3 s, 5 s. | M 2D ROI, Perfusion, PEI, TTP, HAP, PS | MVD of gastric adenocarcinoma is significantly correlated with BV. | Baseline BF is significantly lower and MTT is significantly higher in responders. Baseline BV and PS are not significantly different in responders and non-responders. | Baseline BF and PS decreased after chemotherapy compared to baseline, while MTT increased. |
| Curvo-Semedo et al| 2012 | P          | Evaluate changes in colorectal cancer vascularity following chemotherapy and correlate baseline perfusion and post-treatment using CTP | 20       | Colon Tube voltage: 120 kV; tube current: 300 mA; perfusion scan delay: 5 s | M 2D ROI, BV, BF, HAP, MTT and PS | Baseline BF is significantly lower and MTT is significantly higher in responders. Baseline BV and PS are not significantly different in responders and non-responders. | Baseline BF and PS decreased after chemotherapy compared to baseline, while MTT increased. | Baseline BF and MTT may discriminate responders from non-responders to chemotherapy. |
| Ippolito et al    | 2012 | P          | Assess the role of CTP in detection of BF changes related to the therapeutic effects in HCC lesion treated with RFA | 14       | Liver Tube voltage: 120 kV; tube current: 200 to 240 mA; perfusion scan delay: 8 to 10 s; total duration of acquisition: 23 to 30 s | M 2D ROI, Perfusion, HAP, BV, HAP, MTT and PS | Significant differences in mean values of Perfusion, HAP, and HPI between treated lesions with residual tumor and those successfully treated. | Significant differences in mean values of Perfusion, HAP, and HPI between treated lesions with residual tumor and those successfully treated. | CTP enables assessment of HCC vascularity after RFA treatment. |
| Jiang et al       | 2012 | P          | Investigate the CTP as a biomarker and monitor and predict long-term outcome in advanced HCC treated with RFA | 23       | Liver Tube voltage: 120 kV; tube current: 200 to 240 mA; perfusion scan delay: 8 to 10 s; total duration of acquisition: 23 to 30 s | M 2D ROI, BV, HAP, MTT and PS | After chemotherapia, there is a significant decrease in CTP parameters. Furthermore, tumors with higher baseline MTT values on CTP correlate with favorable clinical outcome and had better 6 months progression-free survival. | CTP is a sensitive biomarker for monitoring early antangogenic treatment effects as well as in predicting outcome at the end of treatment and progression-free survival. | CTP is a sensitive biomarker for monitoring early antangogenic treatment effects as well as in predicting outcome at the end of treatment and progression-free survival. |
| Author et al. | Year | Study type | Aim | Clinical purpose | Patients | Zone | Acquisition details | ROI Info | CTp parameters | Results | Conclusion |
|--------------|------|------------|-----|------------------|---------|-----|---------------------|---------|---------------|---------|------------|
| Kanda et al. | 2012 | P         | Evaluation of liver disease and therapeutic effects with perfusion measurement of 320-detector row CT | Diagnosis/ response to treatment | 38 (10 normal group) and 8 (disease group) | Liver | Tube voltage: 80 kV, tube current-time product: 210 or 250 mA, slice thickness: 5 mm; matrix: 512 x 512; perfusion scan delay: 7-120 s | M 2D ROI | HAP, HPP and AFI | There are no significant differences in the normal group except, AFI for the third and fifth hepatic segments, fundus and antrum. Mean HAP and AFI in disease are significantly higher than the normal group | Perfusion values have the potential for evaluation of liver disease and therapeutic effects |
| Khan et al.  | 2012 | R         | Determine the feasibility of vascular quantification for different anatomical segments of the colorectum | Diagnosis | 39 with colorectal cancer | Colon | Tube voltage: 120 kV, tube current-time product: 60 mAs, perfusion scan delay: 5 s; total duration of acquisition: 63 s | M 2D ROI | BV, BF, MTT and PS | Mean BF is higher in the proximal than distal colorectum. Mean BV is higher, MTT shorter, and PS measurements lower for the proximal colon but this is not statistically significant | The colorectum demonstrates segmental differences in perfusion parameters with tumor grade |
| Kim et al.   | 2012 | P         | Compare pre-operative CTp parameters with tumour grade from CRC and with MVD to evaluate angiogenesis | Diagnosing and staging | 27 [8 with differentiated; 15 with moderately differentiated and 4 poorly differentiated] | Colon | Tube voltage: 80 kVp; tube current: 200 mAs, slice thickness: 5 mm; FOV: 33 cm; matrix: 512 x 512; perfusion scan delay: 5 s | M 2D ROI | BV, BF, MTT and PS | BF is higher in moderately differentiated CRC than well-differentiated and poorly differentiated CRCs. There is no significant difference between well-differentiated and poorly differentiated CRCs. There is no significant correlation between other perfusion parameters and tumor grade | BF and MTT measurement by perfusion CT is effective in predicting moderately differentiated CRCs |
| Yang et al.  | 2012 | P         | Evaluate CTp in the therapeutic response of chemoembolization for HCC | Response to treatment | 24 [12 with a solitary tumor, and 12 with multiple tumors] | Liver | Tube voltage: 120 kV, tube current: 150 mA; FOV: 320 mm; perfusion scan delay: 6 s | M 2D ROI | HAP, HPP, TLP and HAPI | The values of HAP, TLP, and HAPI in tumors 4 weeks after chemoembolization are significantly decreased than those before chemoembolization | CTp evaluate the perfusion changes in HCC after chemoembolization and it can assess the therapeutic response of chemoembolization |
| Chen et al.  | 2013 | P         | Evaluate relationships between BF of HCC measured by CTp and four cirrhotic angiogenic factors | Prognosis | 21 [12 with solitary HCC and 9 with multiple HCCs] | Liver | Tube voltage: 100 kVp; tube current: 240 mAs; perfusion scan delay: 7 s | M 2D ROI | BF | The HCC-parenchyma ratio of arterial BF showed a significantly positive correlation with the level of circulating IL-8 | IL-8 provides a non-invasive tool for assessment of BF in HCC |
| Monbach et al. | 2013 | P        | Assess CTp to predict the morphologic response and survival after TARE | Response to treatment/ survival prediction | 38 with liver metastases | Liver | Tube voltage: 100 kVp; tube current-time product: 150 mAs; perfusion scan delay: 5 s | M 3D ROI | HAP | Significant difference in HAP is found on pre-treatment CTp between the responders and the non-responders to the TARE and a significantly higher 1-year survival after the TARE is found in the patients with a pre-treatment HAP | HAP of liver metastases enables prediction of short-term morphologic response and 1-year survival to TARE |
| Bai et al.   | 2014 | P         | Evaluate relationship between CTp and histopathologic findings in the periphery of HCC lesions | DIAGNOSIS | 77 [47 with HCC and 30 controls] | Liver | Tube voltage: 120 kV, tube current: 280 mAs; slice thickness: 512 x 512; perfusion scan delay: 5 s | M 2D ROI | HAP, HPP, HBF and HAFr | The tumor edges of HCC patients compared to those of the controls | CTp of tumor eddges may be helpful in revealing histopathological features and reflecting angiogenic changes of HCCs |
| Bayrakta˘sta˘n et al. | 2014 | P         | Evaluate the role of CTp in patients with HCC | Diagnosis | 17 with HCC | Liver | Tube voltage: 120 kV, tube current: 150 mA; FOV: 320 mm | M 2D ROI | BV; BF, HAP, and HAPI | BF, BV, HAP, and HAPI are shown to be significantly higher in the HCC lesions than in the surrounding liver parenchyma and HPP is found to be significantly lower in HCC relative to liver parenchyma | CTp has the ability to evaluate tumor assessment, characterization, and neoangiogenesis in HCCs |
| Chen et al.  | 2014 | P         | Investigate microcirculatory differences between pathologic types of kidney tumor using CTp | Diagnosis | 85 [66 with ccRCC, 7 with pRCC, 5 affected by chromophobe and 7 AML with minimal fat] | Kidney | Tube voltage: 100 kV, tube current: 100 mAs; perfusion scan delay: 8 s | M 2D ROI | BF, Equiv BV and PS | Equiv BV is significantly different between RCC and AML with minimal fat and between ccRCC and AML with minimal fat. Mean Equiv BV and BF are significantly higher in ccRCC than in pRCC and mean Equiv BV is higher in ccRCC than in chromophobe RCC | CTp evaluate hemodynamic features of the whole kidney and kidney tumors useful in the differential diagnosis of these four pathologic types of kidney tumor |
| Humam et al. | 2014 | P         | Assess reductions in CT perfusion parameters that can predict response to pre-operative chemotherapy prior to surgery for GEJ and gastric cancer | Response to treatment | 28 affected by adenocarcinoma of the GEJ and stomach | UGI tract | Tube voltage: 100 kV, tube current: 100 mA; 7.5 and 13.5 s; total duration of acquisition: 55 to 60 s | M 2D ROI | BF, BV and PS | Significant changes in PS and tumor volume are apparent after 3 series of chemotherapy in both clinical and histological responders | Early decrease in permeability is correlated with the likelihood of clinical response to pre-operative chemotherapy in GEJ and gastric cancer | (continued)
Table 1. (continued)

| Author | Year | Study type | Clinical purpose | Patients | Zone | Acquisition details | ROI Info | CTp parameters | Results | Conclusion |
|--------|------|------------|------------------|----------|------|---------------------|----------|----------------|---------|------------|
| Ippolito et al | 2014 | P | Determine the value of CTp for the diagnosis and treatment of HCC | Liver | Tube voltage: 100 kV; tube current: 120 mA; matrix: 512 x 512; slice thickness: 3 mm; Perfusion scan delay: 7 s; total duration of acquisition: 50 s | M | 2D ROI | Perfusion, HAP, BV, HAPI and TTP | Significantly lower perfusion values are obtained in correctly treated lesions or surrounding parenchyma than in viable hepatocellular carcinoma tissue | CTp contribute to a non-invasive quantification of tumor blood supply related to the formation of new arterial structures and evaluates the therapeutic response |
| Nishikawa et al | 2014 | R | To find the relationship between TACE and survival of patients with pancreatic cancer | Liver | Tube voltage: 80 kV; tube current: 40 mA; perfusion scan delay: 3 s | M | 2D ROI | BF | There is a significant correlation between post-TACE AUC or BF and survival rates. Higher AUC or BF values are associated with shorter survival but there isn’t any significant correlation between tumoral AUC or BF and survival | The perfusion in pancreatic tissue with proximal pancreatic ducts may be useful in predicting prognosis |
| Reiner et al | 2014 | P | Evaluate CTp for assessment of early treatment response after TACE | Liver | Tube voltage: 100 kV; tube current: 150 mA; perfusion scan delay: 5 s | M | 3D ROI | HAP | Liver metastases show significant differences in HAP before and after TARE in responders but not in non-responders and in HCC, HAP before and after TARE are not significantly different in responders and non-responders | In patients with liver metastases, a decrease of HAP after TARE is associated with a higher 1-year overall survival rate |
| Singh et al | 2014 | P | Determine the role of CTp in differentiating hemangiomas from malignant hepatic lesions | Liver | Tube voltage: 80-100 kV; tube current: 150-300 mA; matrix: 1024 x 1024 mm; slice thickness: 5 mm; Perfusion scan delay: 5 s; Total duration of acquisition: 40 s | M | 2D ROI | BV, BF, MT, MT, HAP, and IRFTO | Significant changes are observed in the perfusion parameters at the periphery of different lesions. Above all BF, HAP, and IRFTO show most significant changes | CTp is a helpful tool in differentiating hemangiomas from hepatic malignancy |
| Wang et al | 2014 | P | Evaluate the value of CTp for the diagnosis of liver cancer | Liver | Tube voltage: 100 kV; tube current: 100 mA; matrix: 1024 x 1024 mm; slice thickness: 5 mm; Perfusion scan delay: 5 s; Total duration of acquisition: 40 s | M | 2D ROI | HBF, BV, HAP, HAPI, and IRFTO | All parameters in liver cancer are significantly decreased after argon-helium knife treatment and there is a significant decrease in HAP observed in peritumoral liver tissue while other parameters kept constant | CTp is reliable to detect decrease in blood perfusion of liver cancer post-argon-helium knife therapy |
| Du et al | 2015 | P | Evaluate the clinical value of CTp in the treatment of HCC | Liver | Tube voltage: 80 kV; tube current: 100 mA; FOV: 300 mm x 350 mm; perfusion scan delay: 3 s | M | 2D ROI | HAP, HAPI, and IRFTO | There is a significant difference in the values of HAP and HAPI between responders and non-responders | CTp shows a significant difference in the values of HAP and HAPI between responders and non-responders |
| Kaufmann et al | 2015 | P | Characterize HCC in terms of perfusion parameters using CTp and two different calculation methods | Liver | Tube voltage: 100 kV; tube current: 120 mA; perfusion scan delay: 7 s; total duration of acquisition: 40 s | M | 2D ROI | HAP, HAPI, HBF, BV, and k-trans | Best correlation between calculation methods is achieved for measurements of BF | CTp can measure tumor volume perfusion non-invasively and enables quantification of the degree of HCC arteriovenous shunting |
| Kaufmann et al | 2015 | P | Response monitoring of TACE with CTp | Liver | Tube voltage: 80 kV; tube current: 100 mA; perfusion scan delay: 7 s; total duration of acquisition: 40 s | M | 3D ROI | HAP, HPI, and HAPI | | CTp accurately measures impact of TACE on liver tumor and hepatic parenchymal perfusion |
| Lv et al | 2015 | P | Evaluate CTp in predicting the early response to TACE and survival of patients with HCC | Liver | Tube voltage: 100 kV; tube current: 120 mA; perfusion scan delay: 7 s; total duration of acquisition: 40 s | M | 2D ROI | HBF, HAP, HPI, and IRFTO | The best cut-off values were −21.5% and patients who achieved a ≥ 21.5% decrease in HAP had significantly higher overall survival rates than those who achieved a < 21.5% decrease | CTp predicts the early response to TACE and survival of patients with HCC |
| Reiner et al | 2015 | P | Assess if the heterogeneity of the HCC response to TARE can be predicted by CTp | Liver | Tube voltage: 100 kV; tube current: 120 mA; perfusion scan delay: 7 s; total duration of acquisition: 40 s | M | 3D ROI | HAP | The histogram analysis of AP values reveals significantly higher values for responders compared to non-responders for the 50th and 75th percentiles of AP values. No significant difference between HAP of responders and non-responders | CTp indicates tumor heterogeneity of HCC and improves the pre-treatment prediction of response to TARE |
| Author              | Year | Study type | Aim                                      | Patients | Zone | Acquisition details | ROIs | CTp parameters | Results                                                                 | Conclusion                                                                 |
|---------------------|------|------------|------------------------------------------|----------|------|----------------------|------|------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Garbino et al.      | 2017 | P          | CTp to detect early therapeutic response in patients with HCC | 28 patients with HCC | Liver | Tube voltage: 120 kV; tube current-time product: 100 mAs; FOV: 4.8 mm; perfusion scan delay: 7 s | M, 2D ROIs | BV, BF, TVP and TTP | BV increase is the most significant perfusional parameter in responding lesions, even at an early stage of therapy, with a high positive predictive value | BV and PS can be indicators of the degree of malignancy and aid in prognostic assessments of gastric cancer |
| D’Onofrio et al.    | 2017 | P          | Perfusion changes in patients affected by liver metastases from PanNETs during everolimus therapy | 9 patients (33 liver metastases) | Liver | Tube voltage: 120 kV; tube current-time product: 100 mAs; FOV: 4.8 mm; perfusion scan delay: 7 s | M, 2D ROIs | BV, BF, PS | Differences between the well-differentiated and the moderately differentiated group are statistically significant for BF, BV, and PS. Differences between the well-differentiated and the poorly differentiated group are not statistically significant. | CTp may predict the response to everolimus in patients with HCC metastases from PanNETs. |
| Kaufmann et al.     | 2017 | P          | CTp to detect early therapeutic response in patients with HCC | 28 patients with HCC | Liver | /                     | /               | BV, BF, PS | Significant decrease is found in BF, BV, and HAPI in patients with SD as well as a significant increase in MTT after two months compared to baseline. PD group show a significant increase in HAPI, BF and BV | Lower BF and BV after two months of sorafenib therapy predict disease stabilization after four months |
| Wu et al.           | 2016 | R          | Examine mVI in patients with HCC with CTp parameters | 56 patients with liver metastases | Liver | Tube voltage: 100 kV; tube current-time product: 100 mAs; FOV: 4.8 mm; perfusion scan delay: 7 s | M, 2D ROIs | BV, BF, TTP and PEI | The tumor PVF, difference in PVF between tumor and liver tissue, and the PVF/liver PVF ratio are significantly higher in sHCC with mVI than in sHCC without mVI | CTp parameters can predict mVI in patients with sHCC |
| Marquez et al.      | 2016 | P          | Assess CTp to examine the treatment response in patients undergoing RFA of focal liver lesions | 20 patients with liver metastases and 10 with sHCC | Liver | Total duration of acquisition: 43 s | M, 2D ROIs | HAP, HPP, HAPI | Mean HAP/HPP/HAPI are 4.8/15.4/61.2 for the CZ, 9.9/16.8/66.3 for the TZ and 20.7/29.0/61.8 for the PZ. Inter-reader agreement of HAPI is fair for the CZ, good for the TZ, and excellent for the PZ. Furthermore, there are significant differences in HAPI of the CZ and TZ between responders and non-responders. | Increased HAPI of the necrotic TZ after RFA might reduce residual tumor in patients with focal liver lesions |
| Su et al.           | 2016 | P          | Assess the role of CTp to predict treatment response to TACE in patients with HCC | 39 patients (46 HCC lesions) | Liver | Total duration of acquisition: 48 s | M, 2D ROIs | HAP, HPP, HAPI | The responders demonstrate higher HAP and lower HPP compared with the non-responders in lesions without portal vein or portal branch thrombosis. | HAP and HAPI are good prognostic values |
| Yadav et al.        | 2016 | R          | Differentiate pancreatic adenocarcinoma from MFCP | 42 patients with pancreatic adenocarcinoma, 13 affected by MFCP and 25 control group | Pancreas | Tube voltage: 100 kV; tube current-time product: 100 mAs; slice thickness: 4.8 mm; perfusion scan delay: 7 s; total duration of acquisition: 48 s | M, 2D ROIs | BF, BV, MTT, TVP and PEI | BF and BV are the most reliable for differentiating between adenocarcinoma and mass-forming pancreatitis. Although they are reduced in both pancreatic adenocarcinoma and MFCP compared to normal controls. | CTp may serve as an additional paradigm for differentiating pancreatic adenocarcinoma from mass-forming CP |
| Zongqiong et al.    | 2016 | P          | The role of CTp in gastric cancer | 71 patients with gastric cancer | UGI tract | Tube voltage: 120 kV; tube current-time product: 100 mAs; FOV: 4.8 mm; perfusion scan delay: 7 s; total duration of acquisition: 30 s | M, 2D ROIs | BV, BF, and PS | Differences between the well-differentiated and the moderately differentiated group or the poorly differentiated are all statistically significant for BF, BV, and PS. | BF and PS can be indicators of the degree of malignancy and aid in prognostic assessments of gastric cancer |
| Xu et al.           | 2015 | R          | Explore characteristics of different gastric cancers on CTp | 50 lesions located in the stomach, 13 in body, and 20 in the gastric antrum | UGI tract | Tube voltage: 120 kV; tube current-time product: 100 mAs; FOV: 4.8 mm; perfusion scan delay: 7 s | M, 2D ROIs | BF, PS, and MTT | BF, PS are statistically significant between the well-differentiated group and the moderate differentiation group. BF, BV, and PS are statistically significant between the well-differentiated group and the poor differentiation group. MTT value show no statistical difference among the 3 groups. Difference between the well-differentiated and the moderate differentiation group are statistically significant for BF, BV, and PS. Differences between the well-differentiated and the poor differentiation group are statistically significant for BF, BV, and PS. | BF and PS values could serve as indicators of the degree of malignancy and aid in prognostic assessment of gastric cancer |
| Sun et al.          | 2015 | P          | CTp for the prognosis assessment of gastric cancer | 50 lesions located in the stomach, 13 in body, and 20 in the gastric antrum | UGI tract | Tube voltage: 120 kV; tube current-time product: 100 mAs; FOV: 4.8 mm; perfusion scan delay: 7 s | M, 2D ROIs | BF, BV, and PS | BF, BV, and PS are statistically significant between the well-differentiated group and the moderate differentiation group. BF, BV, and PS are statistically significant between the well-differentiated group and the poor differentiation group. MTT value show no statistical difference among the 3 groups. | BF, BV and PS values could serve as indicators of the degree of malignancy and aid in prognostic assessment of gastric cancer |
| Sun et al.          | 2015 | R          | Examine mVI in patients with HCC with CTp parameters | 18 patients have shHCC with mVI and 38 patients have shHCC without mVI | Liver | Tube voltage: 100 kV; tube current-time product: 100 mAs; total duration of acquisition: 66 s | M, 2D ROIs | BF, BV, TTP and PEI | The tumor PVF, difference in PVF between tumor and liver tissue, and the PVF/liver PVF ratio are significantly higher in sHCC with mVI than in sHCC without mVI. | CTp parameters can predict mVI in patients with shHCC |
| Pan et al.          | 2015 | R          | Predict the grade of colorectal adenocarcinoma through CTp | 34 patients with colorectal adenocarcinoma; 7 lesions in descending colon; 3 with transverse colon tumor; 3 patients with a lesion in ascending colon and 5 in cecum | Colon | Tube voltage: 120 kV; tube current-time product: 100 mAs; slice thickness: 4.8 mm; perfusion scan delay: 7 s; total duration of acquisition: 66 s | M, 2D ROIs | BV, BF, and PS | There are significant differences in BF and TTP between low and high tumors. | BF and TTP parameters can reflect tumor grade in colorectal adenocarcinoma |

(continued)
Table 1. (continued)

| Author          | Year | Study type | Aim | Patients | Zone | Acquisition details | ROI | CTP parameters | Results | Conclusion |
|-----------------|------|------------|-----|----------|------|---------------------|-----|----------------|---------|------------|
| Marquez et al.  | 2017 | P          | Monitored the perfusion changes in patients with HCC after DEB-TACE | 24 with HCC | Liver | / | M 2D ROI HAP, HPP and HAPI | HPP before DEB-TACE is significantly higher in pre-treated vs non-treated lesions. Mean changes of HAP, HPP, and HAPI from before to after DEB-TACE are −55%, +24% and −27% HAP and HAPI after DEB-TACE are relating with response grades. | The perfusion changes of HCC early after DEB-TACE show incomplete response with good diagnostic accuracy |
| Mohammed et al. | 2017 | P          | Compare the accuracy of washout and CTP in diagnosis of adrenal tumors | 38 (15 patients with adrenal masses were metastases) | Adrenal | Tube voltage: 120 kV; current: 120 mA; slice thickness: 32 mm; perfusion scan delay: 5 s, total duration of acquisition: 55 s | M 2D ROI Perfusion, TTP and BV | BV differentiation adenomas and non-adenomas with an 80% sensitivity, 75% specificity and 77.1% accuracy. | CTP can distinguish from adenomas and non-adenomas using BV; however, without CT was more accurate than perfusion CTP. |
| Popovic et al.  | 2017 | R          | CTP to predict the response to treatment and overall survival in patients affected by HCC and treated with DEB-TACE | 18 patients with intermediate-stage HCC | Liver | Tube voltage: 80 kV; current: 100 mA; slice thickness: 6 mm; perfusion scan delay: 6 s, total duration of acquisition: 55 s | M 3D ROI BV, BF, TTP, HAP, HPP and HAPI | Survival is statistically significantly longer in patients with BF lower than 50.44 mL/100 mL/min, BV lower than 13.32 mL/100 mL and TTP longer than 19.03 s. | CTP predicts survival in patients with intermediate-stage HCC treated with DEB-TACE based on the pre-treatment values of BF, BV and TTP perfusion parameters, but this technique cannot be used to predict treatment response to DEB-TACE. |
| Shabiy et al.   | 2017 | R          | CTPs for diagnosis and monitoring of HCC | 126 patients (141 lesions) | Liver | Tube voltage: 100 kV; current: 60 mA; perfusion scan delay: 4 s, total duration of acquisition: 55 s | M 2D ROI HAP, PB and PF | 41 lesions present 94% sensitivity and 40% specificity with elevated HAP and PEI and with PF. | CTP can diagnose and monitor HCC. |
| Tamandl et al.  | 2017 | P          | Analyze the role of CTP for early response assessment after TACE for HCC | 16 patients (41 HCC) | Liver | / | M 3D ROI BV, BF, TTP, HAP, HPP and HAPI | CTP parameters are significantly reduced after TACE in responders while no difference is shown in non-responders. | CTP detects lesions with complete response one day after TACE. |
| Aslan et al.    | 2018 | P          | Distinguish PDAC from pancreatitis through CTP | 61 cases with PDAC and 12 cases with MFCP | Pancreas | Tube voltage: 100 kV; current-time product: 100 mA; slice thickness: 5 mm; FOV: 300 mm | M 2D ROI BV, BF, MT and PS | Compared with normal parenchyma, BV, BF, PS are lower and MTT is longer in PDAC and MFCP. Compared with MFCP, BV, BF, PS are lower and MTT is longer in PDAC. | CTP can help diagnose PDAC and characterize isoenattenuating lesions. |
| Deniffel et al. | 2018 | P          | Evaluate perfusion parameters of the normal renal and of the renal tumors, extrapolated through different mathematical models | 35 [21: ccRCC: 6; pRCC: 5; oncocytes: 2; angiomyolipoma: 1; tubulocystic: 1; chromophobe: 1] | Kidney | Tube voltage: 100 kV; current 60 to 150 mA; slice thickness: 512 x 512 mm; perfusion scan delay: 6 s, total duration of acquisition: 95 s | M 2D ROI BV, BF and MTT | There are significant differences and poor agreement between BF, BV and MTT for most models in both normal renal cortex and several renal cancers. | BF and BV are a useful tool in the differential diagnosis of kidney tumors using the Park model. |
| Diesky et al.   | 2018 | P          | Assess perfusion changes of liver metastases in patients treated with both bevacizumab and SBRT | 7 patients treated with both bevacizumab and SBRT | Liver | / | BV, BF and PS | After bevacizumab, a significant decrease is found in PS and BV, while with SBRT present a significant reduction in PS and B. | After bevacizumab and SBRT perfusion changes can be studied. |
| Ippolito et al. | 2018 | R          | Evaluate the role of CTPs in the early detection of BF changes correlated to sorafenib in patients with advanced HCC | 41 with liver cirrhosis and intermediate-to-advanced HCC | Liver | Tube voltage: 100 kV; current: 120 mA; slice thickness: 512 x 512 mm; perfusion scan delay: 6 s, total duration of acquisition: 55 s | M 2D ROI Perfusion, HAP, HPP and HAPI | CTP values are significantly higher between baseline and follow-up in the CR and PR groups, while there aren’t significant differences in SD patients and a significant trend toward increase in PD subgroup. | CTP helps to evaluate the therapeutic response to sorafenib in advanced HCC. |
| Liang et al.    | 2018 | R          | Analyze the predictive value of CTP to evaluate efficacy of pre-operative CCRT in middle-aged and elderly patients with LAGC | 60 tumors in gastric Cardia: 27 lesions in the gastric corpus; 28 in the gastric antrum and 11 tumors in the entire stomach. | UGI tract | Slice thickness: 5 mm | BV, BF, MT and PS | Patients with low BF, BV, and PS (compared to cutoff) have longer survival times than these with high BF, BV, and PS. | CTP can predict the pre-operative CCRT efficacy in the LAGC therapy. |
Table 1. (continued)

| Author          | Year | Study type | Aim                                      | Clinical purpose | Patients | Zone | Acquisition details | ROI Info | CTp parameters | Results                                                                                                                                                                                                 | Conclusion                                                                 |
|-----------------|------|------------|------------------------------------------|------------------|----------|------|---------------------|----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Nakamura et al  | 2018 | P          | The role of CTp such as biomarkers       | RESPONSE TO      | Liver    |      | Tube voltage: 80 kV; | M 2D     | HAP and HPP       | Pro-HAP tumor is significantly related to the overall survival rate. The overall survival rate is higher in patients with pre-HAP tumor > 71.7 mL/min/100 mL, and with HAP tumor ratio ≥ 1.1 | CTp can predict overall survival in HCC patients treated with sorafenib, such as biomarker |
| Ng et al        | 2018 | R          | Assess the effects of bevacizumab and   | RESPONSE TO      | Liver    |      | Tube voltage: 80 kV; | M 2D     | BV, BF, HAF, BF,  | In tumor with mono-therapy with bevacizumab, BV is significantly reduced. During dual-therapy, BV and BF are significantly lower than baseline in both arms. No significant effects on CTp parameters in healthy liver | Benazolmab and everolimus have significant effects on CTp parameters in mNETs and healthy tissue |
| Shen et al      | 2018 | R          | CTP to monitor the Sorafenib treatment  | Response to      | Liver    |      | Tube voltage: 100 kV; | M 2D     | HAF, PVI, PEI     | The group of responders to sorafenib shows a significantly decreased HAF value after 2 months compared to that of baseline, while non-responder group shows a significant increase in HAF. Finally, patients with PD show significantly higher HAF compared to that of PD patients | CTP can analyze the Sorafenib effects in HCC lesions                      |
| Andersen et al  | 2019 | P          | Evaluate the CTp parameters during      | RESPONSE TO      | Colon    |      | Tube voltage: 100 kV; | M 3D     | PEI, PS, BV,     | During the treatment, there is a significant decrease of perfusion parameters over time. Changes are shown in the early phase of therapy and this effect is statistically significant over time | There is a significant decrease in most dynamic parameters that highlight an overall treatment effect of regorafenib in tumor vasculature |
| Humdy et al     | 2019 | P          | Study CTp to predict the response of    | RESPONSE TO      | Pancreas |      | Tube voltage: 80 kV; | M 2D     | BV, BF, PVI, HPV  | Baseline BF is higher in responders than in non-responders, while BV and BF are similar between groups | CTp can help predict the histopathological response to therapy in PDAC       |
| Lee et al       | 2019 | P          | Evaluate whether data acquired from     | RESPONSE TO      | UGI      |      | Tube voltage: 80 kV; | M 2D     | BV, BF, TTP, MT   | PS shows a significantly different between the responder and non-responder groups, whereas other CTp parameters do not demonstrate a significant difference | CTP parameters demonstrate predictive value for treatment outcome after palliative chemotherapy |
| Tian et al      | 2020 | R          | Search a correlation between             | Response to      | Liver    |      | Tube voltage: 100 kV; | M 2D     | HAF, PVI, HAPI    | Tumor tissues present higher HAF                                                                                                                                                                      | RAI expression might predict effects of sorafenib in a drained HCC         |
| Zaborien et al  | 2021 | P          | Define the role of CTp in PDAC           | Diagnosis        | Pancreas |      | Tube voltage: 120 kV; | M 2D     | BV, BF, MT, PS   | BF and BV exceed the cut-off therefore the probability of the presence of PDAC is 97.6%                                                                                                                | BF and BV can be independent diagnostic criteria to predict the presence of PDAC |
and 31.5% (18/57) retrospective. Thirty-three studies involved the application of CTp in liver cancer (57.8%), 8 investigated the role of CTp in cancers of upper gastrointestinal tract (14%), 8 were on CTp in pancreatic cancer (14%), 3 on CTp in renal cancers (5.2%), and the remaining 5 were on CTp in colon–rectal cancer (8.7%). To facilitate the reading of Table 1, as well as to provide an organized summary of the CTp parameters investigated in the included studies, a list of perfusion parameters was provided in Table 2 with the corresponding definition and physiological meaning. Refer to Figure 2 for a graphic visualization of the obtained results according to the organs and clinical purposes investigated in the selected studies. Moreover, refer to Table 3 for a schematic representation of CTp parameters investigated in the included studies, according to the specific abdominal area and the clinical purpose.

### Computed Tomography in Liver Cancer

Among studies on liver tumors, fourteen aimed at evaluating the role of CTp for prediction and assessment of response to treatment. Ippolito et al. found that CTp was able to assess HCC vascularity after radiofrequency ablation treatment by means of perfusion, HAO, and HPI features. Similar results were found by Marque et al., even if their study also involved patients with liver metastases other than HCC. Promising results were found by Yang et al. for patients with HCC treated with chemoembolization. Wang et al. found that all CTp parameters investigated in their study were significantly decreasing in HCC after argon–helium knife therapy. Four studies found that CTp parameters were able to assess response to TACE treatment in HCC patients. Results from 3 studies revealed that CTp could help to evaluate the therapeutic response in HCC patients treated with

### Table 2. Summary of Perfusion Computed Tomography Parameters Used in the Included Studies.

| CTp parameter (acronym) | Extended name | Definition | Units |
|-------------------------|---------------|------------|-------|
| BF (or Perfusion)       | Blood flow    | Flow rate in tissue region | mL per 100 g/min |
| BV                      | Blood volume  | Volume of flowing blood in tissue region | mL per 100 g |
| Equiv BV                | Equivalent blood volume | — | mL/100 g |
| PS                      | Permeability surface area-product | — | mL per 100 g/min |
| MTT                     | Mean transit time | Average time taken to travel from artery to vein | Seconds |
| TTP                     | Time to peak   | Time from arrival of the contrast in major arterial vessels to the peak enhancement | Seconds |
| TTS                     | Time to start  | Intervals between contrast injection and the beginning of contrast enhancement | Seconds |
| PEI                     | Peak enhancement intensity | Maximum increase in tissue density after contrast injection | HU |
| HAP                     | Hepatic arterial perfusion | Perfusion of hepatic artery | mL/min per mL |
| HPP                     | Hepatic portal perfusion | Portal vein perfusion of the liver | mL/min per mL |
| HAPI                    | Hepatic arterial perfusion index | HAP/TLP | % |
| HPI                     | Hepatic perfusion index | HAP/(HAP + HPP)*100 | % |
| APF                     | Arterial perfusion fraction | Perfusion percentage of the total blood from the arterial blood supply | % |
| HAFr                    | Hepatic arterial fraction | Percentage of the total blood input from the arterial blood supply | % |
| HAF                     | Hepatic artery flow | Hepatic artery perfusion | mL/min per mL |
| TLP                     | Total liver perfusion | Total perfusion of liver | mL/min per mL |
| K-trans                 | Transit constant | Sum of the flow within the microvasculature and capillary permeability | — |
| PF                      | Portal flow    | Flow of portal vein | mL per 100 g/min |
| HBF                     | Hepatic blood flow | Flow rate in hepatic tissue | mL per 100 g/min |
| HBV                     | Hepatic blood volume | Volume of flowing blood in liver | mL per 100 g |
| HPBV                    | Hepatic portal blood volume | Volume of flowing blood hepatic region | mL per 100 g |
| HPMTT                   | Hepatic portal mean transit time | Average time taken to travel from artery to vein | Seconds |
| PVF                     | Portal vein flow | Flow rate in hepatic tissue | mL per 100 g/min |
| IRFTO                   | Induced residue fraction time of onset | — | Seconds |
| Tmax                    | Transit time to impulse residue function peak | Time to maximum of the residue function | Seconds |
sorafenib. D’Onofrio et al.\(^67\) and Ng et al.\(^79\) evaluated the role of CTp in patients with liver metastases arising from pancreatic neuroendocrine tumors and found that CTp was able to predict response to everolimus and bevacizumab therapy. Similar results were found by Detsky et al.\(^75\) for patients with liver metastases treated with both bevacizumab and stereotactic body radiotherapy. Three studies on liver tumors had diagnostic clinical purpose. Bai et al.\(^47\) found that CTp parameters (BF, HAFr, HAP, and HPP) were able to detect HCC lesion from healthy liver. Similar results were found by Bayraktutan et al.\(^48\) However, their study did not involve control patients, but they used as reference only the surrounding liver parenchyma of HCC patients. Singh et al.\(^53\) found that CTp was a helpful tool in differentiating hemangiomas from HCC and liver metastases. Three studies investigated CTp for prognostic purposes. Kaufmann\(^56\) found that CTp was able to quantify the degree of HCC arterialization. Wu et al.\(^62\) findings were in line with those from Kaufmann et al.\(^56\) since they found that values associated with PVF parameter were able to predict microvascular invasion in patients with HCC. Chen et al.\(^46\) found that arterial BF of HCC lesions was correlated with circulating angiogenetic factors. The remaining thirteen studies had multiple purposes. Specifically, ten investigated CTp for both prognosis and response to treatment assessment of liver cancer and 3 were on diagnosis and response to treatment. Among studies on prognosis and response to treatment, seven were on HCC. Petralia et al.\(^36\) found that BF and BV could predict response to thalidomide treatment and progressive disease. Jiang et al.\(^41\) found that, in HCC patients treated with bevacizumab, CTp parameters were able to monitor treatment effect as well as predict progression-free survival. By means of a histogram analysis of HAP, the work by Reiner et al.\(^59\) revealed that CTp was able to predict response to TARE in HCC. Similar results were also found by Su et al. in HCC patients treated with TACE. Results by Popovic et al.\(^71\) revealed that CTp could predict survival in patients with intermediate stage HCC treated with DEB-TACE. However, this technique was not able to assess response to treatment. Nakamura et al.\(^78\) found that CTp was able to predict overall survival in HCC patients treated with sorafenib. Three studies assessed the role of CTp to predict response to treatment and prognosis in patients with liver metastases,\(^18,52,58\) of which one involved patients with both liver metastases and HCC.\(^52\) Finally, the remaining 3 studies found that several CTp parameters had both diagnostic

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Figure 2. Graphic summary of the systematic review results according to the abdominal zone and clinical purposes investigated in the selected studies. The donut chart shows the number of included studies according to the abdominal zone investigated (liver in orange; upper gastrointestinal tract in yellow; pancreas in green; kidneys in blue; colon/rectum in red). Number and percentage of studies included in each of the five groups were reported in each. For each group, the bar plots show the number of studies according to the clinical purpose investigated. Abbreviations: UGI = Upper Gastrointestinal.
power and were able to predict response to treatment.\textsuperscript{16,42,50} Any study on grading of liver cancer was found.

**Computed Tomography in UGI Cancer**

Considering the 8 articles highlighting the role of CTp in UGI tract, three investigated the power of CTp parameters for grade assessment of gastric cancer and both 3 found that BF, BV, and PS were able to differentiate poor-, moderately-, and well-differentiated gastric cancer.\textsuperscript{60,61,66} Three studies aimed at assessing the role of CTp for response to treatment in patients with UGI cancer, of which two involved patients with gastric cancer\textsuperscript{49,83} and the other one included patients with metastatic gastrointestinal stromal tumors (GIST).\textsuperscript{37} Both found that CTp parameters were able to assess clinical response to different treatment regimens. Yao et al\textsuperscript{38} aimed at evaluating prognosis in patients with gastric adenocarcinoma, focusing on the possible association between CTp and tumor angiogenesis. They found that BV could reflect the angiogenesis due to its significant correlation with microvessel density. The remaining study aimed at assessing both response to treatment and prognosis in patients with gastric cancer by means of CTp parameters.\textsuperscript{77} They found that CTp was able to predict response to concurrent chemo-radiation therapy and survival by means of BF, BV, and PF.

**Computed Tomography in Pancreatic Cancer**

Among studies on CTp role in pancreatic cancer, six had diagnostic purpose and the remaining two aimed at assessing prognosis\textsuperscript{51} and response to treatment\textsuperscript{82} of pancreatic cancer patients. Among diagnostic studies, two were performed by Delrue et al\textsuperscript{33,34} who investigated the utility of 3 CTp parameters (BV, BF, and PS) for differential diagnosis of patients with pancreatic cancer. Specifically, they observed an overall decreasing of BF and BV perfusion values in tumoral tissues with respect to control populations. Similar results were found by Lu et al\textsuperscript{35} who included also TTP and PEI among CTp parameters under investigation, finding promising results also for these features. The power of CTp for differential diagnosis of pancreatic cancer was also highlighted in a recent study performed by Zaboriene et al\textsuperscript{22} who, in a study involving patients with pancreatic ductal adenocarcinoma (PDAC), found that BF and BV were independent predictors of PDAC. Aslan et al\textsuperscript{73} showed that CTp was able to diagnose PDAC and isoattenuating pancreatic lesions thanks to the differences in BV, BF, PS, and MTT values. BV and BF were also found to be useful for the characterization of adenocarcinoma and mass-forming chronic pancreatitis in study by Yadav et al\textsuperscript{21} Concerning works aiming at assessing response to treatment and prognosis, BF was the most significant parameter, with high BF values corresponding to a lower survival and response to treatment.\textsuperscript{51,82}

**Computed Tomography in Renal Cancer**

Similar to what has been found for studies on pancreatic cancer, all 3 studies on CTp for renal cancer applications had diagnostic purposes. Chen et al\textsuperscript{27} found that CTp parameters were useful for differential diagnosis of kidney tumors. Deniffel et al\textsuperscript{74} The third included study involved patients with adrenal tumors and revealed that BV parameter was able to characterize adenomas from non-adenomas.\textsuperscript{70}

**Computed Tomography in Colon–rectal Cancer**

Finally, concerning the five included works focused on CTp for the study of colon–rectal cancer, Khan et al\textsuperscript{43} investigated the role of CTp parameters for quantifying different anatomical segments of colon–rectum. Significant differences were found in BF, BV, MTT, and PS. The same parameters
were investigated to evaluate their association with CRC grade in study by Kim et al. They found that BF and MTT were able to predict moderately differentiated CRCs. These findings were also confirmed by Xu et al. Of note, BF and MTT were also found to be useful for the assessment of response to chemoradiation therapy in locally advanced CRC patients. Finally, Andersen et al. showed the ability of CTp for the assessment of response to regorafenib treatment in patients with treatment-refractory metastatic CRC.

**Quality Assessment**

Based on the QUADAS-2 and QUIPS results, the overall quality of the included studies was considered good for our purposes. The results of the qualitative assessment are shown in Figures 3 and 4 and reported in the Supplementary Materials Tables S1 and S2. Regarding the QUADAS-2 assessment, the risk of bias was classified as low or unclear in all diagnostic studies, for all four QUADAS-2 domains. Concerns about applicability were classified as low across all diagnostic studies. Similarly, for the QUIPS assessment, the risk of bias was classified as low or moderate in all prognostic studies, for all 6 QUIPS domains.

**Discussion**

In this systematic review we aimed at investigating the role and clinical applications of CTp for clinical application in abdominal cancer, including diagnosis, grading, response to treatment, and prognosis. In recent years, the increasing availability and simplicity of CTp, together with its ability in quantification of the abnormal vasculature within tumors led to a growing interest in CTp imaging method for abdominal cancer applications. However, the still present drawbacks, mainly related with the lacking consensus on which CT protocol to use and the fact that published literature is based on small studies with different perfusion algorithms, have resulted in the missing integration of CTp into routine clinical practice protocols for abdominal imaging. In this scenario, we performed a systematic review on the role of CTp in abdominal cancer with a view to provide important new insights and help to reach a common view on the use of CTp for...
several clinical purposes in the management of abdominal cancer. After appropriate inclusion and exclusion criteria, we examined 57 studies from 2011 onwards, evaluating the role of CTp in oncologic diseases of abdominal district. Studies were classified according to the abdominal organ investigated and the clinical purpose explored in the study. Most of the included articles (33/57) deal with CTp at the level of the liver, while a low number of studies investigated CTp for oncologic diseases involving UGI tract (8/57), pancreas (8/57), kidneys (3/57), and colon–rectum (5/57). Interestingly, about 60% of included studies and even about 80% of studies on liver cancer aimed at evaluating the response to treatment of the oncologic patients by means of CTp. This could be related with the urgent need of developing individualized approach, in which the treatment strategies are targeted according to the tumor biology. It is well known neoangiogenesis is one of the key elements of tumor physiology that influences the aggressiveness of cancer and its response to treatment and that the presence of high vascularity usually suggests aggressive behavior and is associated with a poor outcome. Perfusion CT displays and permits quantification of the abnormal vascularity within tumors, specifically hypervascularized tumors such as HCC.24 This was also highlighted in the study by Goh et al86 focused on the therapeutic assessment by means of CTp. Promising results were also found in the field of differential diagnosis of liver tumors, even if the number of studies investigating this issue were poor.47,48,53 Even if only 35% of the included studies were performed on other tumors involving abdominal district, our systematic review revealed that CTp parameters could also help in diagnosis, prognosis, grading, and response to treatment in these areas. Notably, included studies involving patients with pancreatic and colon–rectal cancer had diagnostic purpose. Therefore, a larger number of studies are required to deepen grading, prognosis, and response to treatment in the field of these diseases.

Characteristics of the included studies, such as patient treatment, study aim and setting, CTp parameters investigated, segmentation, and analysis, were highly variable across studies, preventing us from performing a meta-analysis. Moreover, about 30% of the included studies were retrospective, and they are supposed to have more bias and should be validated through prospective studies.87,88 Other important limitations are that the number of patient samples included in the investigated studies was limited and that studies were predominantly single center, thus affecting the generalizability of the results.

To our knowledge, this is the first systematic review aiming at summarizing the role of CTp in abdominal cancer, exploring oncologic diseases of the whole abdominal area. Previous review studies aimed at reviewing clinical applications and technical aspects of CTp.2,89 Kambadakone et al2 reviewed CTp technical aspects and its oncologic and non-oncologic applications. However, this study was not recent and was not focused on abdominal cancer. Bellomi et al89 discussed on CTp in solid body-tumors. However, this study was not systematic and was not specific for abdominal cancer. Notably, Ogul et al8 reviewed the basic principles of CTp discussing both oncologic and non-oncologic applications in abdominal district. Moreover, Hansen et al10 presented an overview of CTp applications in abdominal cancer. However, any of these studies performed a systematic analysis of CTp applications in abdominal district.

Conclusions
In conclusion, our study revealed that CTp could be a valuable functional imaging tool in the field of abdominal oncology. CTp has the potential to play a crucial role in the management of patients with abdominal cancer, particularly as a biomarker for monitoring the response to anti-tumoral treatment. However, data relating CTp features to clinical outcomes remain limited, mainly due to the limited samples and monocentric setting of the studies, as well as the missing consensus about scan protocols for standardized examination. More collaborative research and robust validation are thus required before this innovative technique can be included in routine clinical practice.

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