Tumor Response to Treatment: Prediction and Assessment

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Abstract Neoadjuvant therapy has become part of standard treatment in several types of cancer. Therapeutic effects are often assessed with imaging. The main purpose of response assessment is to define resectability and determine surgical approach. Another controversial purpose of response assessment is selecting patients with complete tumor regression for non-operative strategies. Moreover, response prediction early during treatment can lead to alteration of the initial treatment plan. Another role for pre-treatment imaging lies in the assessment of individual tumor risk profile, to select which patients benefit most from neoadjuvant therapy. Finally, there is a new role for imaging in the guidance of treatment efficacy. This review discusses the different imaging modalities used in clinics to evaluate and predict treatment response in various tumor types. Established response methods such as RECIST and FDG-PET are discussed. Functional imaging

methods such as diffusion-weighted MR imaging, perfusion imaging, and novel PET-imaging techniques are described.

Keywords Tumor response · Neoadjuvant therapy · Chemotherapy · Radiation therapy · Imaging · RECIST

Introduction

Neoadjuvant or preoperative therapy has become part of standard treatment in several types of cancer, especially in locally advanced tumors [1–3]. The purpose of neoadjuvant therapy is to downsize or downstage tumors in order to reduce the rate of local recurrence and improve the surgical outcome, to reduce the risk of distant spread, and improve long-term outcome [4–6]. The role of imaging for the assessment of tumor response after neoadjuvant treatment is substantial. Imaging technology is used in daily clinical practice to monitor the therapeutic effects in solid tumors, e.g., hepatocellular cancer [7], breast cancer [8], head and neck cancer [9], and colorectal liver metastases [10]. The main purpose of response assessment with imaging after preoperative treatment, is to define resectability and determine the surgical approach. The images may furthermore serve as a roadmap during surgery. In patients with complete tumor regression after preoperative treatment, controversial treatment such as deferral from surgery is now being discussed. An example is the management of patients with irradiated locally advanced rectal cancer. Although still under investigation, observational studies [11, 12] have shown that for rectal cancer patients with near complete or complete response after neoadjuvant chemoradiotherapy a standard resection may not always be justified because of the high risk for perioperative

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morbidity and mortality, associated with major surgery. If in the near future non-operative treatment will become routine clinical practice, assessment of response after pre-operative treatment is critical in order to accurately select the eligible patients.

Response prediction early after the onset of treatment can lead to alteration of the initial treatment plan; intensification of treatment in those patients who are likely going to respond, aiming to improve outcome, and eventual discontinuation or alteration of treatment in those patients with obvious disease progression. Another role for pre-treatment imaging lies in the integrated approach for the determination of the individual tumor risk profile. Prognostic biomarkers of response such as imaging biomarkers from functional imaging data allow a personalized treatment stratification according to the patient's individual prognostic profile [13]. Finally, there is a new role for imaging in the guidance of treatment efficacy (theragnostics). New functional and PET imaging provide information on the efficacy of anti-cancer therapies which is important in drug development processes.

This review elaborates on the different imaging modalities used in clinical practice to evaluate and predict treatment response in various tumor types. Established response methods such as RECIST and FDG-PET are discussed. The current role of functional imaging methods such as diffusion-weighted MR imaging (DWI), perfusion imaging, and novel PET-imaging techniques are described.

Response Evaluation After Neoadjuvant Treatment

RECIST and Modified RECIST

Treatment response evaluation in oncology is traditionally based on comparing the size and/or volume of the tumor before and after treatment. A clinically widely adopted measure of response is the "Response Evaluation Criteria In Solid Tumors" (RECIST) system introduced in 2000 [14]. According to this guideline, target lesions are measured in one direction, i.e., uni-dimensional. A review, published 5 years after the implementation of RECIST, showed strong correlations between the response measured with RECIST and the histopathological results for many types of solid tumors [15]. The criteria were revised in 2009 (RECIST 1.1), reducing the number of lesions to be assessed and introducing the assessment of lymph nodes. Additionally, the use of PET-CT was incorporated to detect new lesions [16]. RECIST defines four types of response: [1] complete response defined as a complete absence of disease on imaging, [2] partial response defined as a reduction of ≥ 30 % of the sum of the largest diameters, [3] progressive disease defined as an increase of > 20 % of the

sum of the largest diameters and/or detection of new lesion (incl. FDG-PET), and [4] stable disease, if before mentioned criteria are not met. Figure 1 shows an example of the response of colorectal liver metastases treated with chemotherapy. RECIST has mainly shown good results in solid tumors when evaluating response to "conventional chemotherapy" [17–19]. RECIST is not necessarily representative for changes in tumor volumes in irregular shaped tumors, given the uni-dimensional measurement [20]. Moreover, RECIST does not address any other measurements of anti-tumor changes other than tumor shrinkage. It became obvious that for novel anti-cancer therapeutic agents that do not immediately result in decrease of size, the RECIST guideline is of limited value, good examples of which are the effects of immunotherapy such as bevacizumab in the treatment of colorectal cancer metastases [21, 22], or sorafenib for hepatocellular cancer [23] [24].

To address the issue of tumor necrosis, modified RECIST (mRECIST) criteria were developed [25]. These criteria include enhancement of the target lesions during the arterial phase of either contrast-enhanced CT or MRI. Necrotic areas (non-enhanced during arterial phase) are excluded from the measurement, resulting in a more reliable assessment of the viable tumor remnant [26].

Tumor necrosis can also be assessed by measuring the tumor density, as proposed by Choi et al. [27]. These criteria are generally used in the response assessment of gastrointestinal stromal tumors treated with Imatinib. Partial regression is defined as a decrease in size of ≥ 10 % or a decrease in tumor density of ≥ 15 % (measured in Hounsfield units on CT). Progressive disease is defined as an increase in size of ≥ 10 % and no decrease in density of ≥ 15 % [27].

RECIST criteria are based on uni-dimensional measurements, assuming that tumors are more or less symmetrical and spherical shaped. However, when the tumor length is more than twice the tumor width, measuring longest diameter on its own as a measurement for response will be less accurate. Three-dimensional volume measurements could be more reliable, especially in irregularly shaped tumors. For example, three-dimensional volumetry can accurately predict downstaging after neoadjuvant chemoradiation in locally advanced rectal cancer [28].

FDG-PET

The imaging of tumor metabolic status has found wide applications in cancer diagnostics. Particularly, positron emission tomography (PET) using 2-deoxy-2(^{18}F)-fluorodeoxyglucose (FDG), a glucose analog, is now broadly exploited in the clinics for diagnostic purposes. Due to the enhanced turnover of glucose in the tumor tissue, FDG-

Fig. 1 **a.** Portovenous phase CT of a patient with cT3N2 rectal cancer and synchronous liver metastasis in segment seven and eight. **b.** After two cycles of chemotherapy (capecitabine and oxaliplatin) there is a regression of the target lesions. **c.** After completion of six cycles, the lesion in segment eight is not visible anymore. According to RECIST criteria, partial response (>30 % reduction of sum of diameters) has occurred. Patients underwent right-sided hepatectomy and the histopathology report showed no residual vital tumor (complete response)

PET demonstrates a significant higher uptake in tumors compared to the adjacent normal tissue [29]. Although several different approaches have been advocated to assess FDG-PET for treatment response evaluation, it basically comes down to three strategies: visual estimation of response, semi-quantitative methods, and quantitative kinetic analysis [30]. The first approach entails the visual assessment of increased uptake and the reduction in uptake after treatment. This method is the simplest but—albeit commonly used in clinical interpretations—is not so frequently used in clinical trials as it is subjective and thus highly prone to interobserver variations. Nevertheless, good results have been reported by some groups, for example in the response evaluation of lymphoma and colorectal tumors [31, 32]. The second semi-quantitative method, use of the “standardized uptake value” (SUV) is the most widely applied method to determine the uptake of FDG in tumors. With this technique, the concentration of FDG in the tumor is normalized for the total amount of injected activity and the total volume of distribution within the body (for which often the body weight is used). There are two common ways of reporting SUV values, being either the mean SUV value of all voxels within a given region of interest (SUV_{mean}) or the maximum SUV value measured (SUV_{max}). The benefit of the SUV_{max} is that it is less observer-dependent and therefore, better reproducible. Hence, the SUV_{max} is often considered the best measure of the SUV. Full kinetic quantitative assessment is advantageous compared to SUV measurements since it provides a more absolute measure of the FDG metabolism of tumors. However, for kinetic modeling a precise (arterial) input function is required and its complexity has limited its use in clinical practice.

The commonly observed therapeutic effect when assessing treatment response using FDG-PET is a decrease in SUV, representing a decrease in the proliferative activity of the tumor. Significant decreases in SUV values have been reported as a result of successful treatment in lymphoma, breast cancer, non-small cell lung cancer, esophageal cancer, and colorectal cancer [33]. For example, in a study of 56 patients with non-small cell lung cancer who underwent FDG-PET before and after chemotherapy followed by tumor resection, it was shown that the percentage of SUV inversely decrease correlated well with the amount of residual viable tumor cells at pathology. Using a decrease in SUV of more than 80 % as a threshold, the complete responding tumors could be predicted with an overall accuracy of 96 % [34]. PET-CT also has a major role in the response assessment after treatment for lymphoma, because of its ability to differentiate between fibrosis or sclerosis and residual lymphoma. A PPV and NPV of 100 and 80 %, respectively, have been reported to

detect residual Non-Hodgkin lymphoma after chemotherapy [35].

Diffusion-Weighted Imaging

The assessment of tumor cellular density by diffusion-weighted magnetic resonance imaging (DWI) is one of the most intensively studied therapy evaluation strategies in recent years. This is due to the fact that the majority of current anti-cancer therapies result in the loss of tumor cellularity and DWI has been demonstrated to be sensitive to this effect. Moreover, DWI is a completely non-invasive method, exploiting the tissue water diffusion as an intrinsic MR contrast. Consequently, DWI has been broadly investigated in relation to the prediction, monitoring and assessment of chemotherapy and radiotherapy. Visual evaluation of DWI after treatment has been studied mainly to differentiate between patients with a complete disappearance of malignant lesions versus patients with residual high signal on DWI, indicating persistent tumor. In addition to the visual assessment of DWI, the quantitative parameter of DWI, the apparent diffusion coefficient (ADC) has been the topic of many studies. Changes in the cellularity of tumors as a result of neoadjuvant treatment are reflected by a change in ADC. Typically, ADC values tend to increase as a result of successful treatment. In an animal study of colorectal cancer, the effect of radiation on ADC was measured. Increased ADC was caused by radiation-induced necrosis, and decreased ADC was due to radiation-induced fibrosis [36]. Similar observations have been made in patient studies in several cancer types, including breast cancer [37], liver lesions [38], and rectal cancer [39]. Furthermore, when comparing the changes in ADC after treatment between well and poor responding patients, it is generally observed that well-responding tumors show a more significant increase in ADC after treatment [40].

One of the most studied topics for DWI is response assessment of rectal cancer after neoadjuvant chemoradiation [41–45]. Visual assessment of DWI post-therapy is currently the most promising. For example, it was shown that the diagnostic performance of MRI in detecting a complete tumor response in rectal cancer patients improved significantly from an AUC of 0.66–0.68 when only standard T2-weighted MRI was used to 0.82–0.88 after addition of DWI [42]. Recently, visual assessment of DWI was even recommended in guidelines as part of the standard rectal cancer MR imaging protocol [46]. Figure 2 shows two examples of rectal cancer cases.

In contrast, studies focusing on quantitative assessment of response (ADC) show conflicting results, therefore, ADC measurements post-treatment are not (yet) suitable for clinical applications in rectal cancer [39, 47–50]. DWI has shown promising results for breast cancer [51] and

gynecological cancer (mainly cervical cancer [52]). Although this has not been widely adopted, few centers incorporate DWI in clinical practice of cervical cancer management. A third application of DWI is monitoring response of liver lesions, mostly colorectal liver metastasis [53]. An increasing number of centers have implemented DWI in the standard liver MR protocol, due to the high sensitivity to detect focal liver lesions [54, 55]. There appears to be a role for DWI in the response assessment of lymphoma [56, 57], although PET remains the superior imaging modality since all lymph nodes (both benign and malignant) have a high signal on DWI.

The concept of measuring “average” ADCs using only a limited range of b values is currently being challenged and should perhaps already be considered outdated as recent studies have initiated the search for more comprehensive methods of quantifying ADC. An example is the concept of “intravoxel incoherent motion,” which is based on the notion that ADC measurements are influenced by the movement of water protons both in the extracellular matrix (diffusion), as well as by water motion within (micro) vessels (“pseudodiffusion” or perfusion). When introducing a wider range of b values the effects of perfusion (occurring mainly in the low b value range) and diffusion (occurring at higher b values) may be separately analyzed [58]. Studies are currently also focusing on a voxel-based analysis of ADC and evaluating the distribution of single-voxel ADC values by means of histogram analyses. Such an approach has been shown to provide more detailed information on the tumoral structure than simply measuring the average overall tumor ADC for example in rectal cancer, head and neck cancer, and brain tumors [59–61]. Another important issue is the need for standardization of both the image acquisition and analytic methods of DWI. Basic standards will need to be developed in order for ADC to be broadly adopted in clinical practice as a relevant imaging biomarker.

Perfusion Imaging

Tumor-induced angiogenesis leads to irregular and inadequate perfusion, resulting in the co-existence of metabolically active as well as necrotic tumor areas, and varying degrees of hypoxia. Tissue perfusion can be imaged with dynamic contrast-enhanced MRI (DCE-MRI) and CT (perfusion CT). Anti-angiogenic and anti-vascular therapies, modulating the tumor vasculature, benefit the most from vascular monitoring. The basic principle of perfusion imaging is repeatedly imaging the tumor over time, while the contrast agent is administered. Low-molecular contrast agents such as gadolinium are generally applied in DCE-MRI, and a conventional iodinated contrast agent in perfusion CT. Perfusion imaging has been implemented in

Fig. 2 Standard T2-weighted MRI of two patients with locally advanced tumor (T) in the rectum before (**a**, **d**) and after chemoradiotherapy (**b**, **e**). In both patients, a fibrotic tumor bed after chemoradiotherapy is observed (*black arrows*), which makes it difficult to discriminate between residual tumor and a complete

response. In the upper patient, there is still a clear high signal intensity area on DWI (*white arrows* in **c**), which was confirmed to be a ypT3 residual tumor at histology. In the lower patient, no high signal is shown on DWI (**f**) and a complete tumor response (ypT0) was confirmed at histology

tumor identification, e.g., highly enhancing breast tissue areas are considered as a hypervascular tumor [62], whereas liver metastases display hypovascularity compared to the liver parenchyma [63]. In contrast, the research on response assessment of vascular imaging methods focuses mainly on the feasibility of quantitative vascular parameters (Fig. 3). Tofts et al. [64] described a pharmacokinetic model that has been widely applied, which also takes the arterial input function into account: K^{trans} represents the volume transfer coefficient, and K_{ep} is defined as the contrast rate constant. However, many papers use different quantitative parameters derived from DCE-MRI, this wide variation in parameters makes it more difficult to compare results within the literature. Chemotherapy and radiotherapy, in addition to the cytotoxic effects, induce vascular changes in the tumor. A number of clinical papers reported a correlation between regressive vascular changes in the tumor and positive outcome of neoadjuvant chemotherapy [65–68]. For example, Ng et al. [69] reported an acute increase in vascular parameters derived from perfusion CT, namely Blood Volume (BV) and Permeability Surface area

product (PS), in palliative patients with non-small-cell lung cancer. Furthermore, Mayr et al. [70] found that increasing or persistent high perfusion early in the course of radiotherapy, assessed by DCE-MRI, were favorable signs of response in cervical cancer. However, in a study of the vascular effects of chemoradiation in head and neck cancer, a significant reduction of Blood Flow (BF) and BV was observed for the responders. No significant changes in the vascular parameters were reported for non-responders [66]. Similar observations were reported for rectal cancer patients after the completion of neoadjuvant chemoradiotherapy. Perfusion CT parameters, i.e., BF, BV, and PS, decreased by approximately 50 % after chemoradiotherapy in well-responding patients [67]. Pooled analysis of the diagnostic performance of DCE-MRI for predicting pathologic complete response in breast cancer patients revealed a sensitivity of 0.63 (0.56–0.70) and specificity of 0.91 (0.89–0.92). These results indicate that changes in the vascular parameters may be used to evaluate chemotherapy regimens, predict final pathological response, and select patients for organ-conserving surgery [71].

Fig. 3 Axial T2-weighted image (a) and color-coded K-trans map (b) of the primary MRI of patients with cT3N1 rectal cancer. Axial T2-weighted image (c) and color-coded K-trans map (d) after neoadjuvant chemoradiotherapy. The *arrows* indicate an area of

residual tumor, with high K-trans values. Whereas there is very low K-trans in the area of fibrosis (*arrowheads*). Histopathology confirmed the areas of residual tumor and fibrosis (Color figure online)

Novel PET Techniques

FLT-PET

Considering the key role of tumor cell proliferation in the tumor progression and therapeutic responsiveness, quantitative assessment of the tumor cell proliferation could be useful in determining prognosis, planning treatment, and monitoring response. For this purpose, PET using the radiotracer 3'-deoxy-3'-[^{18}F] fluorothymidine (FLT-PET) has been developed [72]. Most studies of FLT-PET have focused on validating it as means of quantifying cellular proliferation and testing its ability to accurately stage

cancer [73]. Moreover, recent clinical studies have reported that FLT-PET can accurately predict response very early after the initiation of chemotherapy, for example in glioma's [74]. Majority of chemotherapeutic agents reduce tumor FLT uptake as a consequence of cell cycle inhibition. Despite the promising results, the clinical status of FLT-PET is very preliminary.

^{18}F -FMISO-PET

Considering the negative influence of hypoxic tumor areas on the therapy outcome, the assessment of the level of hypoxia as well as its spatial distribution within the tumor

volume could be a useful therapy-planning and prognostic approach. PET using ^{18}F -fluoromisonidazole (^{18}F -FMISO) emerges as the most promising non-invasive method for measuring hypoxia. Tumor to muscle ratio of ^{18}F -FMISO significantly correlated with tumor hypoxic fraction as measured by the polarographic needle electrode [75] and radiotherapy outcome [76] in head and neck cancer patients. Moreover, hypoxic tumors, as concluded from pre-treatment ^{18}F -FMISO, were less likely to poorly respond when treated with a combined chemoradiation and the hypoxic cytotoxic agent tirapazamine (TPZ) when compared to a non-TPZ regimen [77].

Prediction of Response

In line with the postulate on the patient-tailored treatment, the prediction and early assessment of therapeutic response are particularly desired in cancer management. Most results are available for FDG-PET-imaging, but also DWI and perfusion imaging have shown some promising results.

FDG-PET

Many groups have described early SUV effects observed during serial PET scanning that can already be detected starting several days after initiation of treatment. Although the optimal timing of image acquisition during treatment is not yet clear and probably differs depending on the tumor type, this early response assessment appears to be one of the most promising applications of PET. Highly encouraging results have, for example, been reported for colorectal tumors, breast cancer, and lung cancer [78–80]. For rectal cancer, Janssen et al. [80] showed that the final response to treatment could most accurately be predicted based on changes in SUV after two weeks of chemoradiotherapy (AUC 0.87) and that these results were more accurate compared to SUV changes observed later during treatment (just before surgery; AUC 0.66). Moreover, a meta-analysis comparing PET imaging during (e.g., 2–3 weeks after onset of therapy) and after completion of chemoradiation in rectal cancer, showed that PET during therapy has a significant higher diagnostic performance (sensitivity 92 %, specificity 82 %) compared to PET assessment after completion of therapy (sensitivity 80 %, specificity 62 %, $p < 0.05$) [81•]. In NSCLC treated with induction chemotherapy followed by chemoradiotherapy, a SUV_{max} decrease of 60 % measured 2 weeks after completion of induction chemotherapy was found to be highly predictive for long-term survival (5 year survival 60 vs. 15 %, $p < 0.001$) [82]. A recent meta-analysis evaluating the diagnostic performance of PET in monitoring the response of breast cancer to neoadjuvant chemotherapy, reported a pooled

sensitivity and specificity of 73.7 and 85.7 % after one cycle and 76.6 and 84.4 % after two cycles, respectively [83•]. Furthermore, it was shown that the final response to treatment can accurately be predicted based on changes in SUV during the first weeks of treatment and that these early SUV changes may even be correlated with patient outcome in terms of long-term survival [79]. This early response evaluation may be used as a surrogate marker to assess therapeutic efficacy based on which early treatment alterations may be introduced to enhance the treatment response.

DWI

Although the available data are not always consistent, relatively high pre-treatment ADC values have repeatedly been reported to be associated with a worse treatment outcome [44, 84, 85]. In 20 patients with hepatic metastases from colorectal cancer, pre-treatment ADC values were significantly lower in metastatic lesions that responded well to chemotherapy compared to lesions that showed a poor response to treatment [86]. In a study of 20 rectal cancer patients undergoing chemoradiotherapy it was suggested that pre-treatment ADC can accurately differentiate between patients who will undergo a complete tumor response and patients with residual tumor after treatment with a very high sensitivity and specificity of 100 and 86 %, respectively [49]. It is believed that tumors that exhibit high-baseline ADC values are partly necrotic. These necrotic areas (that are associated with tumor hypoxia) are prone to be less sensitive to effects from radiation treatment and cytotoxic agents and are generally linked with a more aggressive tumor profile.

The ADC of tumors is affected by treatment-induced changes in the tumor microarchitecture, which can be detected even early during the treatment process and thereby preceding potential changes in the tumor size and morphology. As such, ADC may be able to analyze response early during treatment before any changes can be visualized on morphology-based imaging methods. Typically, ADC values tend to increase as a result of successful treatment, which is thought to reflect both cell death and necrotic changes [87, 88]. In a prospective study of 37 rectal cancer patients, ADC increased significantly after one week of chemoradiotherapy in patients that showed tumor downstaging, while no significant change was observed in the non-downstaged group [49]. Similarly, in a group of 24 cervical cancer patients, a gradual increase in ADC was observed on serial DWI scans during chemoradiotherapy, which turned out to be significantly associated with the final tumor size response [89].

Decreases in ADC have also been reported shortly after initiation of therapy. These—mainly transient—drops in ADC are believed to be associated with decreases in blood

flow and cell swelling. Moreover, decreases in ADC may be caused by fibrotic tissue changes, as described above. The optimal timing for this early response evaluation, however, remains unclear, and varying effects in ADC (increases and decreases) have so far been reported by different authors.

Perfusion Imaging

Vascular imaging has also been postulated as a promising non-invasive strategy for the planning and early assessment of the conventional anti-cancer therapies. Most reports on the predictive value of vascular imaging have shown that well-vascularized tumors were associated with better regression and local control [90–92]. This correlation has been attributed to the adequate accessibility to chemotherapy and less hypoxia-related resistance in highly perfused tumors. For example, Bellomi et al. [67] examined 25 patients with locally advanced rectal cancer using perfusion CT, and found that the baseline perfusion in 17 responders was significantly higher than in the seven patients who failed to respond to chemoradiotherapy. Similar correlation was reported by several other investigators, who exploited different imaging methods and included different tumor types. Using either DCE-MRI or perfusion CT, they consistently observed a higher baseline vascular function in tumors that displayed a considerable therapeutic response [66, 70, 91, 93–95]. A DCE-MRI study on 17 patients with cervical carcinoma, reported that patients with high-baseline tumor perfusion had a low incidence of local recurrence after radiotherapy [70]. In contrast to the aforementioned findings, several studies have revealed poor outcome associated with highly perfused lesions, possibly, as a consequence of higher aggressiveness [96, 97]. Sahani et al. [68] studied the predictive value of perfusion CT in patients with rectal cancer. They reported that patients with high vascular function responded poorly to neoadjuvant chemoradiotherapy [68]. In breast cancer, most studies showed no statistically significant difference in perfusion parameters before the onset of chemotherapy between good and poor responders [98, 99]. Consistently, high tumor vascularization was reported to negatively impact the long-term patient outcome [96, 100–103]. A study with 105 head and neck cancer patients showed that perfusion CT measurements provided useful predictors of local and regional failure to radiation. Patients with a perfusion rate lower than 83.5 mL/min/100 g rate had a significantly higher local failure rate [91]. In breast cancer, Pickles et al. [96] investigated the predictive value of DCE-MRI data with regard to long-term survival. The study on 54 cases demonstrated that in patients who exhibited high levels of perfusion and vessel permeability in the primary tumor, a significantly lower disease-free survival and overall survival occurred after neoadjuvant

chemotherapy, followed by surgery. The results of these studies support, therefore, the hypothesis that less-perfused tumors respond poorly to radiotherapy.

Changes in tumor perfusion early during neoadjuvant treatment to predict tumor response have also been reported. Mayr et al. [70] found that increasing or persistent high perfusion early in the course of radiotherapy, assessed by DCE-MRI, were favorable signs of response in cervical cancer. Also for breast cancer, it has been reported that higher tumor vascularization after two cycles of chemotherapy, as depicted with DCE-MRI, was associated with higher recurrence and lower survival rates in patients with advanced breast cancer [101]. A systematic review on DCE-MRI studies measuring reduction in K^{trans} and tumor volume, usually after one–two cycles of chemotherapy, showed appreciable diagnostic performance for the prediction of complete and near-complete pathological response, although this was mainly focused in tumor volume [65]. Some studies have been performed on DCE-MRI in rectal cancer, a significantly increased vascular function in the first and second week of treatment compared to the baseline level was observed. Subsequently, in the week 3 and 4, vascular function returned to pre-treatment level or showed further increase [97].

Conclusions

Neoadjuvant therapy aims to downsize or downstage tumors and has been widely applied in the treatment of several types of cancer. This review discusses the different imaging modalities used in daily clinical practice to evaluate and predict treatment response and elaborates on upcoming functional imaging modalities.

The most common clinical application is the use of RECIST criteria as a measure of response. These criteria, based on the largest diameter of target lesions, have shown good results in solid tumors treated with “conventional” chemotherapy. However, the RECIST guideline is of limited value when assessing tumor response after treatment with novel anti-cancer therapeutic agents such as immunotherapy and anti-angiogenic therapy. Therefore, modified RECIST criteria were developed to address necrosis by means of contrast-enhanced CT or MRI. The Choi criteria represent tumor necrosis by measuring tumor density in addition to diameter.

With FDG-PET, the metabolic status of tumors can be imaged, typically showing a decrease in metabolic activity after therapy. The semi-quantitative SUV has been observed to decrease after therapy in good responding patients with lymphoma, breast cancer, non-small cell lung cancer, esophageal cancer, and colorectal cancer.

Biomarkers from functional MR imaging do not (yet) play a significant role in daily clinics. Visual assessment of DWI has been widely investigated in the response assessment of

rectal cancer after neoadjuvant chemoradiation, and it was recently recommended as part of the restaging MR protocol in patients treated with preoperative chemoradiotherapy [46]. However, no consensus has been reached on quantitative ADC measurements for rectal cancer response assessment. DWI has also shown promising results for patients with breast cancer, colorectal liver metastasis, cervical cancer, and to a lesser extent, with lymphoma.

Perfusion imaging (DCE-MRI and perfusion CT) is particularly suited for response assessment after treatment with anti-vascular therapies. Due to different (semi) quantitative parameters explored in the literature, it is difficult to compare the results. Additionally, some papers report an increase in perfusion in good responding patients, while other authors report a decrease in good responders. Microvascular changes as a result of treatment may vary depending on both tumor type and treatment regimens. This technique is not (yet) ready for clinical practice and validation in large patient studies, needs to be performed.

Response prediction and early assessment of therapeutic effects would allow for patient-tailored treatment. However, current available imaging modalities with promising results are still under investigation. For the response assessment early during therapy, no consensus exists on the optimal timing of imaging and probably differs per type of cancer.

FDG-PET is the most studied modality for the early prediction of response to therapy. Promising results have been reported for colorectal cancer, breast cancer, and lung cancer. Generally, a decrease in SUV is observed. Imaging biomarkers of functional MRI like pre or during treatment, ADC has shown promising results for colorectal liver metastases, rectal tumors, and cervical cancer. Significant increase in ADC during treatment is observed in patients who are likely going to respond. Most evidence, however, is still from single center data, and multicenter studies are lacking. The studies on perfusion imaging as a predictor of response have been for rectal cancer, cervical cancer, head and neck cancer, and breast cancer. The results, although promising, are still preliminary and not applicable for clinical practice.

Novel imaging techniques, such as FLT-PET for quantifying tumor cell proliferation and ^{18}F -FMISO-PET for measuring hypoxia, are still in the preliminary phase, but seem very promising for response prediction.

Compliance with Ethical Guidelines

Conflict of Interest Dr. Milou Martens, Dr. Doenja Lambregts, Dr. Ewelina Kluza, and Prof. Dr. Regina Beets-Tan each declare no potential conflicts of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance;
- Of major importance

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