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Imaging beyond RECIST: CT and MRI in molecular therapies

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Abstract

Until recently, almost all systemic antineoplastic therapies in cancer patients aimed at destruction of tumor cells, i.e. they were cytotoxic. The effect of therapy was assessed by measuring the tumor size with a decrease in size suggesting response to therapy and an increase suggesting progression. Modern molecular therapies, however, are mostly not cytotoxic but aim to reduce tumor perfusion or metabolism by blocking specific cell functions without causing cell death. Assessment of tumor size alone may, therefore, not be appropriate in this setting and can even lead to false conclusions. This presentation gives examples of changes at computed tomography (CT) and magnetic resonance imaging (MRI) of tumors undergoing therapy with molecular therapies, highlights potential pitfalls und suggests criteria for response assessment. The presentation focuses on CT and MRI of chest and abdominal tumors and specifically excludes positron emission tomography/CT and brain tumors.

Keywords: *Computed tomography; magnetic resonance imaging; molecular therapy; tyrosine kinase inhibitor; pseudoprogression; RECIST criteria.*

Introduction

Medical therapy for malignancy is currently undergoing significant change from standard chemotherapy to personalized medicine with targeted (molecular) therapies. As a result, the radiologic appearances of tumor manifestations during therapy change and the criteria for assessment of response to therapy have to be adapted.

The first tumor in which targeted therapy was introduced into clinical routine is the rare gastrointestinal stromal tumor (GIST) treated with the oral tyrosine kinase inhibitor (TKI) imatinib (marketed as Gleevec™ in the United States or Glivec® in Europe). Information collected in this model can now be transferred to molecular therapy in other more common tumors such as lung, breast, colorectal, renal, hepatocellular, pancreatic and other cancers, some leukemias and lymphomas.

The aim of this review is to present examples of radiologic findings during targeted therapies at computed tomography (CT) and magnetic resonance imaging (MRI), as these represent the modalities most commonly used for radiologic response assessment. Other aspects such as positron emission tomography (PET)/CT or brain tumors are not included.

Cytotoxic chemotherapy

Traditional chemotherapy aims at inhibition of cell growth and division. It is effective only in proliferating cells and does not selectively attack malignant cells. Therefore, it is usually associated with side effects in benign cells, most commonly affecting those with active proliferation (bone marrow, gastrointestinal mucosa, hair, etc.). It does not affect non-proliferating tumor cells. Therefore, chemotherapy is usually repeated in order to treat tumor cells that were not proliferating during previous therapies.

As chemotherapy causes cell death and, after degradation of necrotic cells, actual shrinkage of tumor

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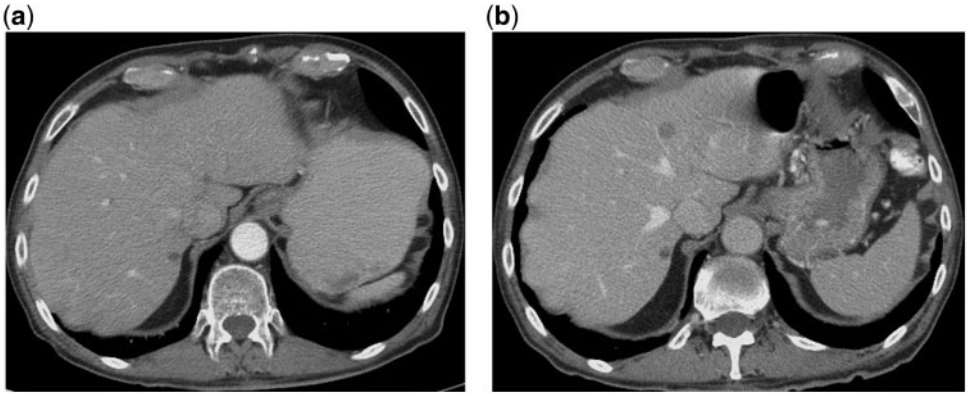

Figure 1 **An 81-year-old man with colorectal cancer and liver metastases before (a) and after (b) initiation of therapy with bevacizumab (Avastin™). A lesion in segment 7 is identified before and after initiation of therapy, a lesion in segment 4A, however, is seen only after initiation of therapy.**

manifestations, the tumor size, measured as the maximum diameter (Response Evaluation Criteria in Solid Tumours (RECIST))[1,2], two perpendicular diameters (World Health Organization (WHO) classification) or more recently with three-dimensional volumetric techniques, is considered to reflect response (decrease in tumor size or volume), progression (increase in tumor size or volume) or stable disease.

Targeted (molecular) therapy

Targeted therapy aims at inhibiting specific targets in tumor cells by attacking cellular components that are exclusively or predominantly present in tumor cells but not or to a lesser extent in benign cells. These drugs are mostly monoclonal antibodies acting at cell surfaces or small molecules that can act at the intracellular level. The latter can block cellular processes such as proliferation or gene transcription by interfering with the action of different enzymes (tyrosine kinases, serine/threonine protein kinases, farnesyltransferase, etc.). Several other small molecule inhibitors are under development. The interaction between the agent and the tumor cell most often does not cause cell death but inhibition of metabolism, perfusion and, thus, proliferation. Therefore, if therapy is discontinued, the cells may resume their metabolism and proliferation. In effective molecular therapy, tumor size may be stable or even apparently larger (see below). Response assessment, therefore, includes other findings such as glucose metabolism at PET/CT (not included in this review), myxoid degeneration, decrease in perfusion, etc.

Imaging findings in molecular therapy

Due to the different effects of molecular therapies on tumor manifestations, some of the imaging findings are quite different from the well-described findings with cytotoxic therapies[3]. These findings are likely to indicate biological effects of the drug on the tumor and may, therefore, be used during early-phase clinical trials to demonstrate interaction between the drug and the tumor. For some findings, a correlation with patient outcome has been demonstrated, e.g. correlation between the Choi criteria (see below) and time to progression. Thus, these findings can be utilized to tailor therapeutic concepts and predict prognosis.

Pseudoprogression

Depending on the imaging modality used, malignant tumors and their metastases may exhibit soft tissue attenuation (CT) or signal (MRI) identical to the surrounding normal tissue, e.g. in the liver. Therefore, the lesion may be completely undetectable at imaging studies such as contrast-enhanced CT or T1-weighted MRI or their periphery may be indistinguishable from the surrounding tissue with only demarcation of a necrotic center. If perfusion decreases in these lesions due to (effective) systemic therapy, they may become visible as hypodense or hypointense structures (Figs. 1a,b and 2a,b) at contrast-enhanced CT or MRI.

In this specific situation, demonstration of a lesion that was not identified before therapy represents actual response, whereas using conventional criteria such as RECIST, demonstration of a new lesion would be classified as progression. Also, lesions responding with a decrease in perfusion to systemic therapy may appear larger as an initial isodense or isointense periphery may become hypodense or hypointense and, thus, distinguishable from the surrounding tissue (Fig. 2b,c).

Therefore, the term pseudoprogression was suggested in this situation and care should be taken to correctly assess the effect of therapy. It can be helpful to look for the apparently new lesion at the baseline examination with different techniques such as narrow windowing at CT or different sequences other than T1-weighted at MRI to possibly identify their presence in retrospect.

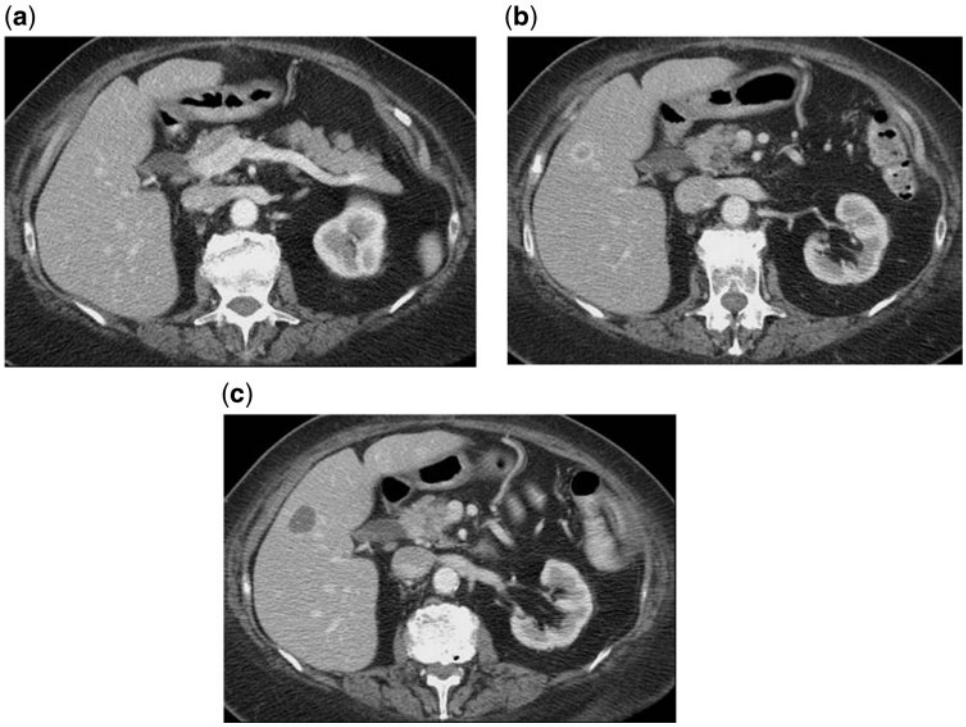

Figure 2 **A 74-year-old woman with GIST and liver metastases before (a), 2 months (b) and 5 months (c) after initiation of therapy with imatinib (Gleevec™).**

Choi et al.[4] described this effect in GIST tumors undergoing therapy with a TKI (imatinib; Gleevec™) and suggested revised criteria for response assessment in which an increase in size accompanied by a significant decrease in density (>15% of Hounsfield units) at CT is reported as response.

Changes in attenuation of normal liver parenchyma

Some targeted therapies for colorectal liver metastases can decrease global liver enhancement in the portal venous phase while not changing the baseline attenuation of liver parenchyma[5]. This is different from the induction of liver steatosis following cytotoxic therapy, which decreases overall liver attenuation. As a result, tumor-to-liver contrast can deteriorate, decreasing the conspicuity of metastases during therapy.

Hemorrhage

Several modern compounds used for molecular therapies may cause spontaneous hemorrhage into the treated tumor, which often leads to an increase in tumor size, and which in this case, obviously, does not represent progression. It is, therefore, mandatory to include techniques in imaging protocols that allow for detection of hemorrhage, such as unenhanced CT or unenhanced T1-weighted sequences at MRI. This is particularly important if the clinical symptoms are suggestive of hemorrhage, e.g. sudden onset of pain during therapy (Fig. 3a,b).

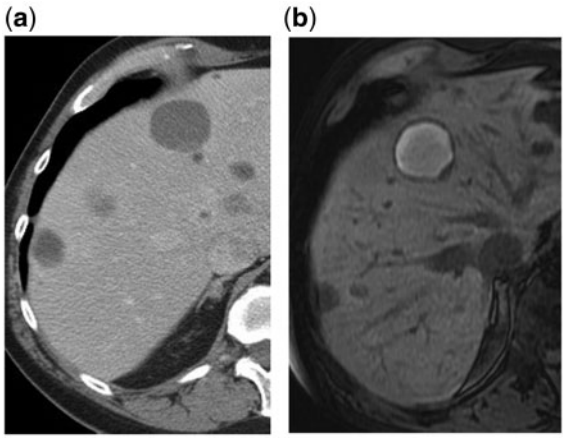

Figure 3 **A 61-year-old man with GIST and liver metastases. All metastases appear hypodense at contrast-enhanced CT (a). One metastasis is hyperintense at T1-weighted MRI (b) due to spontaneous hemorrhage into the metastasis.**

Nodule in a cyst

In GISTs undergoing therapy with TKIs, a phenomenon was reported first in which a tumorous lesion initially responded to therapy with a decrease in density/signal

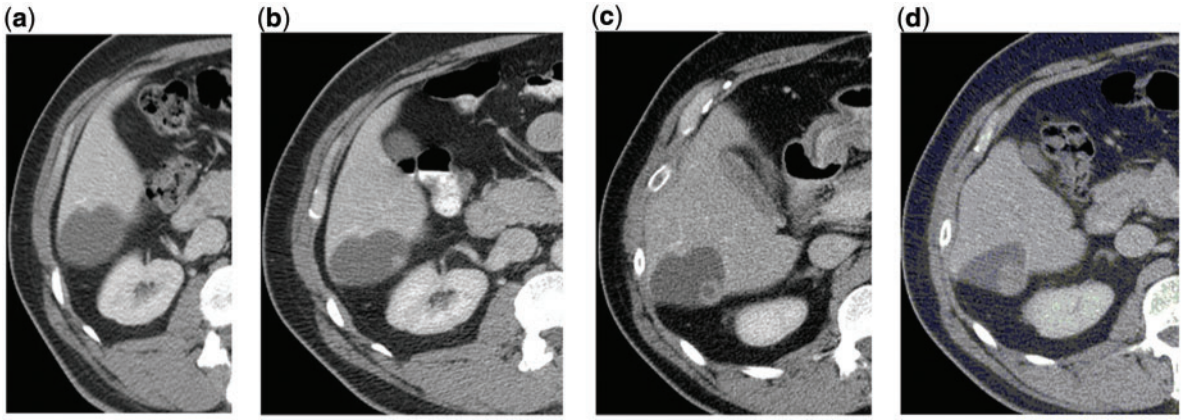

Figure 4 **A 55-year-old man with GIST and liver metastases on imatinib therapy. Purely hypodense lesion at baseline (a), new soft tissue density lesion (nodule) within the cyst after 9 months (b) with further growth after 18 months (c) and 27 months (d) representing progression.**

with or without decrease in size. Later a nodule with increased density/signal developed within the hypodense/hypointense lesion without an increase in the overall size of the lesion representing progression (Fig. 4a–d). This imaging finding was named nodule in a cyst with the hypodense/hypointense lesion representing the cyst and the new solid lesion the nodule. Thus, it is important to carefully look for soft tissue density/signal lesions within hypodense/hypointense lesions with unchanged size during follow-up.

Cavitation

During targeted therapy with anti-angiogenetic agents, cavitation may occur indicating response. Overall tumor diameter may, however, not change. Therefore, conventional measurement of diameter or overall volume may not be appropriate to describe response. It has been suggested to subtract the cavitary portion of the tumor from the overall volume in this setting[6].

Conflict of interest

The author has no conflicts of interest to declare.

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