Evaluation of tumour response to treatment in Oncology: from buzzwords to radiological report.

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Learning objectives

1) Provide a practical, clinically-relevant summary of key imaging issues in common cancers.

2) Provide an overview of current cancer-related terminology, definitions and 'buzz' words used in everyday practice.

3) Learn how imaging can optimally assess and measure tumor treatment response, providing a value-added radiology report.
Background

In Oncology, imaging is critical because all decisions concerning the treatment strategy (start, stop, change, treatment modalities) rely on the combination of clinical, biological and imaging data.

Therefore, imaging is the main pillar of evaluation in oncology, because it reliably assesses tumours that are stable or are responding on one hand, tumours that are progressing on the other hand. Imaging provides measurable and comparative information.

Clinical data are important in order:

- to adjudicate some difficult situations like the uncertain imaging results
- to help evaluating some lesions that imaging can hardly reach and/or measure (skin lesions, some superficial lymph nodes, bone metastases)
- to assess pain related to bone metastases
- to examine specific metastases
- to evaluate Performance Status.

Biology might be important in some cases, when a well-established biomarker provides reliable information on tumor activity, but this is by far not the commonest situation.

Therefore, imaging is the most reliable, reproducible and standardized method for tumor evaluation.
Imaging findings OR Procedure details

Communication between the different specialists is mandatory and should be facilitated by common language and shared standards. WHO criteria have been proposed initially. Basically, WHO criteria applied to any method, including X Rays and clinical examination, but had been defined before the era of CT and MRI. Also, WHO criteria became a more heterogeneous group since in many protocols modified versions of WHO criteria were presented, which is deleterious for the comparison of studies. RECIST have been described more recently (1) and paralleled the availability and development of helical CT. RECIST is also a rather unique concept and there are no modifications until now, allowing a better comparison between studies; Finally, RECIST considers only the largest diameter of the tumour, while WHO was based on the product of both longer diameter (long axis) and longer orthogonal diameter (short axis). First revision of RECIST occurred in 2009 (2), changing mainly the required number of targets, and the method for measuring lymphadenopathies (3).

Ever since, attempts have been made to improve the evaluation of response to treatment, using manual or automated 3D measurements of the tumours (4), or even the association of size and other morphological criteria (5, 6). However, none system proved to be a better compromise between accuracy and simplicity.

Today, RECIST, despite recognized limits, is the basic system for evaluation of tumour response. The radiologist should be familiar with it and learn how to integrate this standard simply and rapidly in their report.

A/Definitions:

Some words should be precisely understood and properly used.

Response:

Response is considered as a positive evolution of the lesion according to International criteria. It can be a complete disappearance of the lesion, also called complete response [CR], or a decrease of more than 30% of the longest tumour diameter, also called partial response [PR].

However, this term is sometimes understood as the global tumour evolution when treated, whatever is the result. In this case, Progression is also one response!

Progression
Progression is a very important term. It is usually reported as progressive disease [PD]. It does not correspond to any subjective impression but conversely relies on very precise words and standards:

- for measurable disease (see this term below), Progression corresponds to an increase in more than 20% in the longest diameter of the tumor, if only one target has been chosen, or in the sum of longest diameter of all targets if several tumors have been chosen for measurements.
- For non-measurable disease (see this term below), Progression corresponds to an unequivocal increase of the lesions size. Of course this is partly subjective, however, the term "unequivocal" is important and provides more reliability to this assessment. This means that any reader looking at the images would share the impression of an increase. If not unequivocal, the lesion should not be considered as a progression, but rather as an undetermined lesion that should be followed up.
- Appearance of New Lesions is also a sign for Progression. Once again, the term "unequivocal" should be written in the report. If not, the lesions should not be considered as a new lesion. they should be reported within the "ambiguous findings" section of the report and will be submitted to further follow-up.

Because progression is very important invents and means usually that the treatment has failed and should be replaced, the Radiologist should be very careful in assessing PD. When unsure, the clinician will usually decide for the treatment strategy according to clinical data and also to the presence or absence of adverse events related to the treatment.

**Targets, Measurable disease:**

Targets are defined as lesions that will be measured from the beginning of the treatment to the end, in order to evaluate the response. According to the most recent recommendations, in case of multiple lesions, a maximum of two lesions should be measured per organ, and a maximum of five lesions if several organs are involved (2).

It is a good idea to include targets that are representative of the tumour burden, both in size and in spread.

In many patients receiving chemotherapy, there are multiple lesions, and usually many more than two per organ may qualify for being a Target (Figure 1). Therefore the experience of the Radiologist will be important in order to choose the appropriate lesions that suit best the evaluation.
It is also important to provide sufficient details in order to find easily the lesion that was measured. This will save a lot of time during the sequential evaluations of the patient. In the selected image can be saved as "Key images" or even embedded within the report. If this possibility is unavailable, reporting the slice location will in any case facilitate the retrospective search.

Measurable does not mean only that the tumor can be measured. It means that the measurements of the lesion will be easy, reproducible, and reliable. It is usually recommended to choose the lesions with clear cut margins, with the maximum diameter larger than twice the slice thickness, in order to avoid any ambiguity related to partial volume effect. It is also preferable to choose larger lesions than smaller lesions, because this will minimize the measurement error.

Choosing a target may be difficult because in some cases, there are some confusing images related to the surrounding parenchyma like perfusion abnormalities of the liver (figure 2) or lung condensation around the tumor.

In most cases the international standard used is RECIST [Response evaluation Criteria In Solid Tumor]. It consists in the measurement of the largest diameter of the tumor (figure 3). When there are several targets, the diameter of each is added to others and the final sum of these diameters is the only indicator. The effect of the treatment will be evaluated on the evolution of this sum of diameters. Response and progression will be determined, based on the changes in diameter as compared to baseline for response and Nadir [see below the definitions of these terms] for progression.

Based on the measurements of target lesions, the patient will be therefore classified as CR, PR or PD. if the measurements do not provide criteria for CR, PR or PD, the patient will be considered as having a stable disease [SD]

In the patient with no lesion fulfilling these criteria, an evaluation can still be performed. However, in the absence of measurements, there will be no possibility to call a partial response.

Bone metastasis could almost never be considered as measurable disease, even if technically it could be sometimes easy to measure the maximum diameter of the lesion. The evolution of bone disease is different from other lesions, and, by definition, bone metastasis will be considered as non-measurable disease (Figure 4,5).

Non-measurable disease and Non-Targets
As opposed to target lesions that should always be measurable, non-target lesions are a group of tumors with very different characteristics:

- Some are too small to be considered as measurable, under the threshold which is usually 1 cm in diameter.
- Some are measurable, but it the reasons add already been chosen to be the representative targets.
- Some are really impossible to measure: this is the case of effusions, infiltrating lesions (figure 6), lymphangitis or carcinomatosis of the peritoneum or pleura.
- As said previously, bone metastasis are always considered as non-measurable disease. An exception is the soft tissue mass arising from the bone, but developing mostly or exclusively out of the bone. (figure 7,8)

Nevertheless, all these lesions participate in the evaluation of the response.

However, due to absence of measurements, the category "PR" is not applicable to non-targets. Although it is sometimes obvious that all non-targets have improved, without disappearing, these cases cannot be classified as partial responses. By definition, they are reported as "SD".

A complete response could be set if all the tumors disappear, and a progression is decided if an unequivocal increase in size of non-target lesions is found.

In all other cases the non target response to will be SD.

**Baseline and Nadir:**

By definition baseline is the examination that is performed before the treatment begins. It is extremely important that the delay between the examination date and the real start of the treatment is very short, especially in fast-growing tumours. The explanation is simple: even the delay between imaging and treatment stopped is too long the lesion may have changed, increased, and new lesions may have appeared. In this case the first evaluation after the onset of the treatment will falsely compare with a baseline study not representative of the real extent of the tumor when initiating the treatment. The figures 9,10 and 11 illustrate such a situation.

Nadir is the best results of the treatment. When targets are available, it is simply determined as the evaluation with the smallest sum of target diameters.
Therefore, any evaluation should be compared both to baseline assess the response and to nadir in order to assess a potential progression. It is sometimes assumed that the previous examination is always a good substitute for Nadir. This is not always the case, as explained in Figures 12 and 13.

**A patient is responding and progressing in the same time: What is the decision?**

It should be noticed that in many cases the patient can be both responding as compared with baseline and progressing as compared with nadir. This is illustrated in figure 14. When this is the case, the final decision is a progression, because any growth of the tumor, even if it does not reach yet the initial size, indicates treatment failure. Another pitfall is the risk to delaying the progression determination in case of slow growing tumors. In this case, give the comparison is only made with the premise evaluation, there will be no significance increase in size. However if we come back to the real nadir, it appears that the progression is a significant.

**B/ What are the useful endpoints?**

The endpoints are tools for global evaluation of the treatment and comparison with other studies. The Radiologist should understand the meaning of the terms in order to give a clear answer to the clinician and the researcher.

**Response Rate:**

This endpoint explores the percentage of patients with a CR or PR in the treated population.

**Disease control rate:**

This endpoint explores the percentage of patients without PD in the treated population. As compared with the previous one, stable disease is associated to PR and CR because in oncology, it is considered that stability of the tumor is a favourable effect of the treatment. This is especially important now, because the targeted therapies to not use the high percentage all CR or PR's, but conversely increase the number of stable disease.

**Best overall response (BOR)**
This endpoint explores the "depth" of the treatment. If, at a first evaluation, the patient is progressing, the BOR will be PD. If the best response is SD, whatever is the number of evaluations, the best response will be SD.

If the patient had a PR or the CR, the best overall response will be PR or CR if, and only if, this response has been confirmed by a second examination made at least one month later. If this is not the case and if only one time point was able to show the CR or PR, the best overall response will be downsized in PR and SD respectively. "X" means that there is no evaluation, because once a PD has been called, the treatment should change. Remember: "Once PD, always PD"

Here are some examples

<table>
<thead>
<tr>
<th>Response at Evaluation 1</th>
<th>Response at Evaluation 2</th>
<th>Response at Evaluation 3</th>
<th>Response at Evaluation 4</th>
<th>BOR</th>
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<tbody>
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<td>PR</td>
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**Best Overall Response (BOR)**

Note that there is absolutely no relationship between the quality of the response and the overall control of the disease. Line 1 shows a patient with a good response (confirmed PR), though conversely a progression at evaluation 3, while line 2 shows a patient with only stable disease, but the treatment is still ongoing and presumably the patient is still doing well after 4 evaluations. On line 3 the patient has reached CR, but, as it was not confirmed by a second consecutive evaluation, the response was downsized into a PR. On line 4, although the patient is progressing rapidly, the first evaluation was SD and so is the BOR. In line 5, the patient is PD at the first evaluation, and the BOR is PD.

**Time to Progression (TTP)**

Today, TTP is probably the most important endpoint. It explores the duration of disease control, whatever is the quality of the response. As exposed in the BOR paragraph, the quality of the response is not necessarily related to the duration of the treatment efficiency. This is a common situation in case of targeted therapies. These treatments do not destroy the cells, but prevent the tumour from developing and spreading, most
commonly by means of impaired angiogenesis. The number of patients with PR or CR is low, while the number of patients with prolonged SD increased. TTP seems to be better correlated with overall survival than endpoints related to the quality of response like BOR or Response Rate.

The definition of TTP is the time elapsed between the beginning of the treatment and tumour progression or cancer-related death. Meanwhile the patient might be CR, PR or SD.

There are two variants:

- **Time to Recurrence (TTR):** this applies to patients who had a curative treatment and are submitted to follow-up. Many are given an adjuvant regimen. TTR is the time elapsed between the initial treatment and the detection of recurrence.
- **Progression Free Survival (PFS):** this endpoint explores the time elapsed between the beginning of the treatment and either progression or death. This endpoint is different from TTP for two reasons: in TTP, the final event is related to cancer. In PFS, death can be related to adverse events, or also to a disease not directly related to cancer. In some tumours like hepatocellular carcinoma (HCC), TTP and PFS might be very different due to the expected high number of patient dying of cirrhosis, and not from HCC. This applies also to patients with a significant co-morbidity, like lung cancer or ENT tumours, presenting commonly with severe atherosclerosis.

However, it is not always very easy to determine if death in totally, partially, or not at all related to cancer, which means that PFS is more "inclusive" than TTP, but conversely does not explore specifically the outcome related to the tumour.

**Survival**

Of course, survival is supposed to be the best and the most reliable endpoint. However, this is not the case in many patients for several reasons. First, from cancer detection to death, the patients will have been commonly treated with several consecutive regimens. Therefore, it is difficult to say if a prolonged survival is related to a specific line of treatment and to a specific drug. Second, some patients fortunately experience a very prolonged survival, and it will take years before the benefit of an alternative treatment is proven.

**C/ Basic tips for the report:**

**Baseline Report**
Baseline examination is different, because it is the first examination for a specific regimen. Its role is to describe extensively all lesions and to determine which one will be selected as targets or non targets, according to RECIST.

Other findings are listed, including benign lesions. The conclusion indicates clearly the sum of largest diameters.

**Further Evaluations report**

The radiological report of an evaluation examination should be structured, short and informative.

It should answer the following questions and only those:

1. **What is the sum of target diameters?**
2. **Are the Non Target lesions qualified for CR, PD or are they SD?**
3. **Are there any unequivocal new lesions**
4. **Are there any questionable lesions that should be looked at specifically at next evaluation as new lesions deemed too small to be unequivocal for a progression yet?**
5. **Are there any concomitant lesions requiring attention or treatment, like pulmonary embolism or infection?**

The question # 4 is important, and should be very clearly answered within the report. It happens that some new images are ambiguous. On one hand, these images are seen and consistent with new metastases. On the other hand, they are either not specific (tumor? Infection? Other?) or even disputable. Because the consequence would be to change the treatment, it is impossible to take this decision without a minimal certainty. Usually, there is no need for further examinations (like MR or PET). The most pragmatic matter to handle these cases is to indicate clearly in the report that some lesions are uncertain, and that they should be carefully scrutinized on the occasion of next evaluation before a final decision is taken(Figure 15,16).

Other lesions already known from baseline should not be commented extensively. Liver or kidney cysts, arterial calcification and all other ancillary findings will not change nor require a specific treatment.
Fig. 0: This patient had Liver Metastasis from a pancreatic cancer located in the tail. Because there are many metastases, the Radiologist should choose a maximum of two, with a priority to those with clear boundaries and the largest diameter, to ensure the quality of the Follow-Up

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Fig. 0: Hepatocellular Carcinoma. This patient has a large tumour with clear boundaries; however, the medial margin is rather geographic, suggesting that some vascular abnormalities can be associated and might impair measurability. If the lesion is unique, there is no other solution than including this lesion as a target. However, during following examinations, attention to be paid to the morphology of changes in order to see if these modifications are related to tumor size only.

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Fig. 0: Technique for Target measurement and assessment of sum of diameters. Two targets were chosen in the liver. The longest diameter of each tumor are measured. These diameters are added and provide the final sum of diameter. This sum will be the reference for target evolution. If the patient has other targets in other organs, the diameters should as well be added.

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**Fig. 0:** Bone metastases from breast cancer. baseline examination. There is a round lytic area in the middle of the body of the thoracic vertebrae. Although the limits are clear and measurability is technically easy, this lesion should be considered as a non-target.

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Fig. 0: Bone metastases from breast cancer. Evaluation after 8 cycles of chemotherapy. The attenuation of the bone lesion has increased, which is consistent with re-calcification and probably improvement. However, the size of the lesion has not changed as compared with baseline. As a Non-Target, this lesion is rated "SD".

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Fig. 0: Diffuse infiltrating Hepatocellular carcinoma. The boundaries of the lesion are unclear. This lesion is non measurable

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**Fig. 0:** Sternal metastases from breast cancer. Baseline examination. This metastases clearly originates from bone, although it might be challenging to decide if bone is involved secondarily or is the primary site. This mass is almost completely developed out of the borders of the sternum, and could be measurable. This is the only case in which bone metastases can be considered as measurable. Even rib metastases, which sometimes develop.

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**Fig. 0:** Same patient as Figure 7. Examination performed after 12 cycles of chemotherapy. The soft tissue mass has dramatically decreased, but not disappeared. This is a Partial Response.

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Fig. 0: baseline CT showing liver metastasis in a woman suffering from ovarian cancer

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Fig. 0: Evaluation at three months in the same patient than figure 4. There is now ascites and new lesions infiltrating the periphery of the initial liver lesion.

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Fig. 0: Evaluation at six month. Same patient and figure 4 and 5. The treatments did not change after evaluation want [see figure 5] because the treatment was well supported and though was also obvious clinical improvement. Looking back at baseline, it appeared that that was a two-month delay between baseline and first treatment. It is likely that ascites and liver lesion growth had occurred between imaging and the real date of initial treatment.

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Fig. 0: Evolution of the sum of diameter at baseline and 4 evaluations, [time point 1 to 4]. The nadir is the evaluation with the best result under treatment. When there are targets, Nadir occurs when the sum of diameters is the smallest. When the progression is rather fast, The nadir is usually the most recent examination, but it is not always the case. On this diagram, it appears that the nadir happens at the second time point, while the progression is called at the third time point.

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**Fig. 0**: Evolution of the sum of diameter at baseline and 4 evaluations, [time point 1 to 4]. In this case the tumor is growing slowly. The nadir is seen at evaluation one [TP1]. On the following examination, the patient does not reach the threshold for progression at TP2. At TP 3, the progression is significant [+ 25%] has compelled to nadir, but not significant [+15%] as compared with the previous examination. However, the treatment should be stopped at this evaluation. If the results of an evaluation is only compared to the premise examination and not to the nadir, there is a risk for a significant delay in determination of the progression, which means that the treatment is not optimal.

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**Fig. 0:** Patient with common cancer and metastasis to the liver. The baseline examination shows several lesions. The treatment was initiated in January. In April, there is an obvious partial response. In October, there is an obvious progression. Examination performed in July was considered as a response because it had been compared to baseline. However, the Nadir was April, and July examination should have been considered as the progression. They line is the reference for restaurants. Nadir is the reference for progression. When the patient, like this one, fulfills both criteria for restaurants [as compared with baseline] and progression [as compared with nadir], hr should be considered as progressive. A new treatment should have been introduced in July, without waiting for major progression as observed in October.

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Fig. 0: A patient treated for rectal cancer and previous surgery for lung metastasis. Follow-up examination detected a potential recurrence within the left lung. However, the lesion was small and it was decided to wait for another follow-up, with the usual 3 month delay.

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Fig. 0: Same patient as Figure 15. This examination was performed three month later. The left lung lesion has unequivocally increased, which was consistent for recurrence of lung metastasis. Interestingly, PET-CT was negative. Surgery was again decided.

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Conclusion

Whatever are the limits of RECIST, it is the only standard applicable to most situations today. Even if we can anticipate that new drugs and new post processing tools will allow a more personalized and predictive analysis of tumor response, RECIST will remain as well the common ground on which additional methods will flourish. Hopefully, imaging biomarkers will develop.

Today, Radiologists need to understand these criteria and make the best use of them. This is a first step towards necessary standardisation, as well as simplification of routine examinations in patients with cancer.

Detection of Progression of the disease appears to be the most important role for the radiologist, because in all other situations, CR, PR or even SD, there is no real real consequence on the treatment strategy.

Not only the radiologist should be able to detect the progression as early as possible, but he should also provide information for the strategy, based on the specificity of this findings, either because the images are clear and a decision can be be made immediately, or because images are uncertain and Follow-Up is mandatory.

Understanding endpoints will also participate in the improvement of the dialogue between the radiologists and the referring clinicians. The radiologist should be a first line partner for trials.


