Staging colorectal cancer with the TNM 7th: The presumption of innocence when applying the M category

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Abstract

One of the main changes of the current TNM-7 is the elimination of the category Mx, since it has been a source of ambiguity and misinterpretation, especially by pathologists. Therefore the ultimate staging would be better performed by the patient’s clinician who can classify the disease M0 (no distant metastasis) or M1 (presence of distant metastasis), having access to the completeness of data resulting from clinical examination, imaging workup and pathology report. However this important change doesn’t take into account the diagnostic value and the challenge of small indeterminate visceral lesions encountered, in particular, during radiological staging of patients with colorectal cancer. In this article the diagnosis of these lesions with multiple imaging modalities, their frequency, significance and relevance to staging and disease management are described in a multidisciplinary way. In particular the interplay between clinical, radiological and pathological staging, which are usually conducted independently, is discussed. The integrated approach shows that there are both advantages and disadvantages to abandoning the Mx category. To avoid ambiguity arising both by applying and interpreting Mx category for stage assigning, its abandoning seems reasonable. The recognition of the importance of small lesion characterization raises the need for applying a separate category; therefore a proposal for their categorization is put forward. By using the proposed categorization the lack of consideration for indeterminate visceral lesions with the current staging system will be overcome, also optimizing tailored follow-up.

INTRODUCTION

Stage IV colorectal cancer (CRC) is no longer considered a single entity[1] and after several proposals for stratifying it[2,3] the current TNM-7 subdivides the M1 category into M1a (metastasis confined to one organ: liver, lung,
of cure at presentation and those for whom only palliative treatment is possible.[6]

An other major change with the new TNM-7 is that the category “MX: Distant metastasis cannot be assessed” has been eliminated[8].

In this report, the change with the TNM-7 is discussed in a multidisciplinary setting and the diagnostic significance of small indeterminate visceral lesions encountered during radiological staging of patients with colorectal cancer is presented.

The resulting problems, in particular the ambiguities for stage assigning when applying the MX category and the risk of inaccurate staging and follow-up planning because of its elimination, are discussed. A proposal is presented for the categorization of such small, indeterminate visceral lesions.

**RADIOLOGICAL STAGING**

The major task of radiological staging is the exclusion (cM0) or detection (cM1) of metastases, particularly in the liver and/or the lung. The most frequently used imaging modalities for staging of CRC cancer patients are ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT (PET/CT).[9,10] In the past 10 years, important advances have been made within all four techniques. While some (CT and PET/CT) will give patient specific information regarding abnormal masses and increased tissue metabolic activity throughout the body, others (MRI) will yield organ (liver) specific information and allow characterization of specific abnormalities to differentiate benign from malignant lesions. However, no single modality will diagnose all metastases, and the optimal imaging strategy to classify cM0 or cM1 depends on the clinical context, the organ site investigated, and the individual aims of oncologic care.

With the introduction of multidetector row CT (MDCT) scanning, CT imaging will continue to play the dominant role in the radiological staging of CRC patients.[14] Improved MDCT technologies have resulted in increased CT detection of small (< 1 cm) indeterminate lesions in the lung and/or liver (in around 10%-40% of CT CRC staging examinations).[15-20].
A major drawback of MDCT is that its ability to detect small lesions has outstripped its ability to characterize them. Although most tiny lung and/or liver lesions detected on CT staging of CRC patients are benign (Figure 1), 10%-20% of CT-indeterminate lung and/or liver lesions do develop into definite metastases (Figure 2)\textsuperscript{[17,18,20,21]}. The M stage of CRC patients with CT-indeterminate lung and/or liver lesions, therefore, would require the category MX (“X” meaning uncertainty).

Regarding the definite diagnosis of whether or not these lesions are benign or malignant, consideration should include the T stage and the nodal status of the primary tumour and the distribution patterns of lesions as the probability of malignancy of small lung or liver lesions depends on the stage of the primary tumour (T stage) and the nodal status (N stage)\textsuperscript{[17,18]}.

Further evaluation with complementary imaging modalities is needed in patients with small CT-indeterminate lesions if a change of M staging would alter the treatment. In the thorax, additional PET/CT may be helpful in the differentiation of a single < 1 cm pulmonary lesion, but it may not be efficient when more than one small lesion is found on MDCT examination. In the liver, US may be the primary modality of choice in cases of advanced liver metastases, whereas contrast-enhanced US\textsuperscript{[22]} MRI\textsuperscript{[23,24]} and/or US-CT fusion imaging tech-
CONCLUSION

**Advantages and disadvantages of the revised TNM classification of metastatic status**

Disease management for CRC has evolved in recent years into a multidisciplinary setting and is essentially based on tumour stage.

Cancer staging represents the operational basis for choosing the most appropriate therapy and for evaluating the efficacy of different therapeutic methods; it is an essential component of patient care, cancer research, and control activities, even in light of the impressive progress that has been attained in the fields of clinical strategies and molecular medicine.

The TNM system is subjected to continuous updating through an ongoing expert review of existing data.

Proposals for changes are made in different situations, including when the classification is poorly accepted, poorly used, or criticized in the literature[27]: here comes the decision for MX category elimination[6].

As the MX category results in ambiguity (lack of information or uncertainty in assigning a given category) both in applying and in interpreting it for stage assigning, it seems reasonable to abandon it.

This is also in accord with the general rule of the techniques[25] may complement the initial CT information in candidates for liver resection.

Follow-up CT imaging may be a reasonable approach in patients in whom a change of M staging would alter the clinical management, as malignant lesions would be expected to grow but benign lesions less so.

During restaging after neoadjuvant chemotherapy, besides the complete clinical remission (disappearance on CT, ycM0) achieved in a small number of patients with metastases (mainly in CRC lung or liver metastases), small lesions, suspected as being residual tumour may be encountered (Figure 3): the difficulties in interpreting these lesions are made harder by the response to chemotherapy which may impact on the sensitivity of preoperative imaging studies in identifying all sites of disease[26].

Either chemotherapy itself, or the fatty infiltration it commonly causes, can affect the ability of CT to effectively restage patients, resulting in both false negative and false positive results; thus, in patients with known hepatic steatosis, or in patients receiving neo-adjuvant chemotherapy, liver MRI is often recommended for staging or restaging of hepatic disease[14].

However, only pathologic examination can determine the actual nature of these lesions (Figure 4).
TNM system which states that, “if there is doubt concerning the correct category to which a particular patient should be allotted (T, N, or M), then the lower (i.e., less advanced) category should be used”[46]. However, the increased detection of small indeterminate lesions due to improved imaging technologies, particularly with MDCT imaging[26], suggests that a separate category is needed.

This is to avoid the application of M0 category to all indeterminate/suspicious lesions, with consequent reduced diagnostic accuracy and staging errors.

Proposal
Cancer patients with small indeterminate lesions (e.g., in the lung and/or liver) are at risk of developing metas- tases and therefore need continued follow-up with imaging. The TNM staging system uses an extensive number of prefixes and suffixes, as additional descriptors, their presence indicating cases needing separate analysis[4] and ongoing investigation. We propose to add a suffix (e.g., iPUL, iHEP) to cM0 to indicate the presence of "small indeterminate lesions" considered to be benign but to be surveyed on further follow-up imaging to confirm that they are benign by their unchanged size and radiologic characteristics.

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