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The pathologist and the colorectal cancer in 2010

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The pathologist belongs to the multidisciplinary team responsable for the patient, and high-quality pathology reports are essential in providing accurate prognostic information and guiding the different steps of optimal patient management.

In initial treatment decisions, histological diagnosis is still mandatory to decide the therapeutic regimen, especially in rectal cancer, before neo-adjuvant therapy: there is a higher risk of involved resection margins due to understaging of rectal mucinous carcinoma on imaging.

After the local treatment, (polypectomy of pedunculated lesions, mucosectomy), careful examination of orientated, inked in toto specimens, is necessary to evaluate the risks of recurrence and systemic disease, such as deep margins, differentiation of the tumour, vascular invasion and budding.

After surgery, pTNM classification remains the gold standard of colorectal prognostic factors. This classification, developed in the 40ties by a french surgeon (Pierre Denoix), has been constantly improved and the seventh edition (2010) is the last one. "T" relates to the primary tumour, "N" to the regional lymph nodes, and "M" to the distant metastasis. " R", given by the circumferential margin (R1 when CRM < 1 mm of the mesorectal limit), reflects efficacy of initial treatment, strongly influences adjuvant treatment, and is mandatory in rectal cancer: it is a strong prognostic indicator, independent from stage.

The number of lymph nodes is crucial: 12 is considered as "minimal" by most surgeons and oncologists, and directly influences the prognosis for stage II. But numerous factors influence this number: the patient individual variations (obesity, age), the tumour (differentiation, preoperative radiotherapy), the pathologist (assistant versus senior), the surgeon…

The pathologist can help the genetician. Fifteen percent of colorectal cancers have microsatellite instability, with a better prognostic and distinct sensitivity to chemotherapy. Immunohistochemistry on a formalin fixed paraffine embedded tissue is the ideal method to detect mutations of MMR genes: hMLH1, hMSH2, hMSH6.

In the choice of targeted treatment, immunohistochemistry of the protein EGFR has failed to predict the efficacy of drugs, but K-RAS mutations can be studied on paraffine materiel, and are a predictor of resistance to anti EGFR antibodies therapy and are associated with a worse prognosis.

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Predictive factors in colorectal cancer

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Colorectal cancers do not represent a homogeneous entity and two main pathways are involved in their pathogenesis: the microsatellite instability (MSI) and the chromosomal instability (CIN). CIN tumours are more likely to bear *APC*, *TP53* or *KRAS* mutations compared to MSI tumours. Furthermore, the rate of *BRAF* mutations is significantly higher in sporadic MSI tumours with methylated *hMLH1* promoter than in other MSI (Lynch syndrome) or CIN tumours. Some of these molecular features are prognostic and/or predictive, and their identification is today necessary in some settings.

In patients with stage III disease, the combination of oxaliplatin and fluoropyrimidines is the standard, and is used in most patients. In stage II colon cancer, the absolute improvement of overall survival with fluoropyrimidines adjuvant chemotherapy is statistically significant but small. Thus, it does not support the use of adjuvant chemotherapy in all patients but only in those with high-risk stage II disease. Concordant and accumulated results of independent large studies allow to admit that MS status is a robust prognostic factor in colon cancer. Moreover, patients with stage II and III MSI tumours do not benefit from fluoropyrimidines alone, and, consequently, MS status should be determined before all adjuvant chemotherapy decisions with fluoropyrimidines alone.

In metastatic setting, three targeted therapies have proved their efficacy in phase III randomized studies. Among them, cetuximab and panitumumab are two monoclonal antibodies that target epidermal growth factor receptor (EGFR). Subsequently to their development and use, many studies have focus on EGFR pathway, and many potential predictive factors have been investigated as *Kras*, *Braf* and *PI3KCA* mutations, *EGFR* amplification, PTEN expression, or EGFR amphiregulin and epiregulin ligands' expression. Nevertheless, at present, *Kras* mutation status is the only predictive factor used in routine practice, and its determination is required before all anti-EGFR prescriptions.

The progress of molecular biology on one hand, and the development of targeted therapies on the other have opened a new era in digestive oncology. Soon, the necessity of tumour and/or patient molecular features' determination will certainly increase, allowing to individualize our treatments.