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Position Paper

Gastrointestinal lymphomas: French Intergroup clinical practice recommendations for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFH)☆

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ABSTRACT

Introduction: This document is a summary of the French Intergroup guidelines on the management of gastro-intestinal lymphomas, available on the web-site of the French Society of Gastroenterology, SNFGE (www.tncd.org), updated in September 2017.
Methods: This collaborative work was realised under the auspices of several French medical societies and involved clinicians with specific expertise in the field of gastrointestinal lymphomas, including gastroenterologists, haematologists, pathologists, and radiation oncologist, representing the major French or European clinical trial groups. It summarises their consensus on the management of gastrointestinal lymphomas, based on the recent literature data, previous published guidelines and the expert opinions.
Results: The clinical management, and especially the therapeutic strategies of the gastro-intestinal lymphomas are specific to their histological subtypes and to their locations in the digestive tract, with the particularity of gastric MALT lymphomas which are the most frequent and usually related to gastritis induced by *Helicobacter pylori*.
Conclusion: Lymphomas are much less common than epithelial tumours of gastro-intestinal digestive tract. Their different histological subtypes determine their management and prognosis. Each individual case should be discussed within the expert multidisciplinary team.

1. Introduction

Primary gastro-intestinal lymphomas (PGIL) are non-Hodgkin lymphomas (NHL) derived from MALT (Mucosa Associated Lymphoid Tissue) [1]. PGIL are rare, corresponding to 1% of all gastro-intestinal tumours. Their incidence varies among different countries between 0.58 and 1.31/100,000 inhabitants and the usual age of diagnosis is between 50 and 70 years [2,3]. Stomach is the most frequent site of these lymphomas, followed by the small intestine and the colon [4]. Both B and T lymphocytes may give rise to PGIL, but B-cell lymphomas are much more frequent (90%) than T-cell lymphomas (10%.)

PGIL comprise different clinico-pathological entities which should be distinguished since their cellular origins and clinical presentations determine their evolution and treatment. Rare prospective studies taking into account the recent classifications and proposing standardised treatments [4–6], improved our knowledge on these lymphomas. Although gastro-intestinal locations represent 36% of the extra-nodal forms of NHL, these tumours remain rare, which, together with the great diversity of their anatomo-clinical forms and their sometimes slow progression, explain the difficulty of developing randomised therapeutic trials

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specific to the digestive localisations. In consequence, the indication of chemotherapy in the chemo-sensitive forms comes mainly from randomised studies performed in nodal NHL which are much more frequent. The recent recommendations, like those published by the European Gastro-Intestinal Lymphoma Study Group (EGILS) [7] or by the European Society for Medical Oncology (ESMO) [8,9], concern essentially gastric lymphomas and derive mainly from the results of small series or expert opinions.

The clinical management of the PGIL, and particularly the therapeutic strategies, are specific to their histological types and to their location in the digestive tract, with the particularity of gastric MALT lymphomas which are the most frequent and usually related to *Helicobacter pylori (H. pylori)* — induced gastritis.

2. Methodology

This collaborative work was realised under the auspices of several French medical societies and involved clinicians with specific expertise in the field of gastrointestinal lymphomas, including gastroenterologists, haematologists, pathologists, and radiation oncologist, representing the major French or European lymphoma study groups. It summarises their consensus on the management of gastrointestinal lymphomas, based on the recent literature data (original publications, prospective non randomised studies, reviews), previous published guidelines and the expert opinions [7,8]. The recommendations outlined below do not generally fulfil the criteria for high level evidence since no prospective randomised trials are available in the field of this rare disease. The two levels of recommendations, designed as "recommendations" or "options", are mainly based on expert opinions.

3. Diagnosis

The diagnosis of lymphoma is based on histology and should be always confirmed by an expert pathologist [7]. In France, a second histological analysis by an expert pathologist belonging to the national group of expert pathologists for lymphomas (LYMPHOPATH), is mandatory for all types of lymphomas.

For histological diagnosis, several biopsies must be obtained (10–20) from the tumour area and additionally from the normally looking antral and corpus mucosa (for the assessment of the presence of *H. pylori* and associated lesions, like atrophy and intestinal metaplasia). The biopsies are fixed in formalin for histological, immuno-histochemical and molecular analysis. Frozen biopsies are not necessary for routine diagnosis but can be recommended for clinical research. More rarely, the diagnosis is made during emergency surgery performed for complications, like haemorrhage or obstruction (especially for lymphomas located in the small intestine) [10].

For gastric forms, testing for *H. pylori* is mandatory. The method of choice is histology, based on the assessment of biopsies taken from the antrum and from the body, away from mucosal lesions, performed using Giemsa or cresyl violet staining, and if necessary, completed by immuno-histochemistry with anti-*H. pylori* antibodies. In case of negative histology, serology is recommended, and this is the only indirect diagnostic test not affected by proton pump inhibitor (PPI) or antibiotic treatment. The ^{13}C-labelled urea breath test is useful for confirming the eradication of bacteria after the treatment. Moreover, the molecular methods, and in particular a real-time PCR may be used for *H. pylori* detection. This method has excellent sensitivity and specificity, it also allows the detection of mutations associated with macrolides resistance, and it does not require specific conditions for the transport of the biopsies. However, there have been no larger studies testing PCR in patients with MALT lymphoma but only some case reports have been reported [11].

The *H. pylori*-positive status is defined as a positive histology and/or a positive serology [12]. It should be noted that histology, ^{13}C-urea breath and culture should be performed after an interval of at least 4 weeks from any antibiotic treatment and at least 2 weeks after stopping the PPI [12,13].

Table 1
Different histopathological types of gastrointestinal lymphomas (according to WHO classification 2016, Ref. [11]).

B Lymphomas
• Extra-nodal marginal zone of the Mucosa Associated Lymphoid Tissue: MALT including alpha Chain Disease (IPSID)
• Diffuse large B-cell
• Mantle cell
• Burkitt
• Follicular
T Lymphomas
•Associated or not with an intestinal-type enteropathy (with or without villous atrophy) of low and especially high grade of malignancy

4. Histomorphological classification

The different types of primary lymphomas of the digestive tract were initially described by Isaacson [1], but currently the latest 2016 WHO classification for all NHL is considered the reference and diagnosis should be given according to this classification [14]. It takes into account the cellular origin of the proliferation, determined according to morphological and immuno-histochemical criteria (Table 1).

The most frequent are B-cell lymphomas (90% of cases), and very rare T-cell lymphomas. The majority of PGIL originate from MALT. In Western countries, gastric lymphomas are the most frequent and they are represented by two major types: extra-nodal marginal zone lymphomas (MZL-MALT, also called MALT lymphomas), corresponding to the proliferation of small B-cells, and diffuse large B-cell lymphomas (DLBCL), composed of large B-cells, usually developed de novo, but sometimes evolving from transformed MALT lymphomas. In the intestine, all the varieties of NHL, similar to the nodal types, can be found.

In extra-nodal gastric MALT lymphomas, after eradication of *H. pylori* and for the follow-up, the histological results are given according to the GELA (Groupe d'Etude des Lymphomes de l'Adulte) histological scoring system [15] (Table 2).

Because of important prognostic and therapeutic implications, the histological sub-type of the lymphoma must be accurately established. The opinion of expert pathologists, reviewing the slides

Table 2
Histological scoring system of GELA for the post-treatment assessment of gastric MALT lymphomas (According to Copie-Bergman et al. [15]) .

Score	Lymphoid infiltrate	LEL	Stroma
CR	Absent or scattered plasma cells and small lymphocytes in LP	Absent	Normal or empty LP and or fibrosis
pMRD	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
rRD	Dense, diffuse or nodular extending around glands in the LP	Focal or absent	Focal empty LP and/or fibrosis
NC	Dense, diffuse or nodular	Present — May be absent	No changes

CR: complete histological remission; pMRD: probable minimal residual disease; rRD: responding residual disease. NC: no change; LP: lamina propria. MM: muscularis mucosa. SM: submucosa. LEL: lymphoepithelial lesions.

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