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Watch and wait policy in advanced neuroendocrine tumors: What does it mean?

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Abstract

Neuroendocrine neoplasms (NENs) are a group of rare and heterogeneous malignancies, which can develop in various organs. The clinical course of NENs is quite

heterogeneous, with different spontaneous growth rates after diagnosis, and different degrees of sensitivity to the same therapy even when they have similar characteristics. *Watch and wait* (W and W), is a term coined to indicate observation being conducted to assess the evolution of the tumor without administering any anti-tumor therapy. It has been applied to NENs since in extremely rare cases they tend to remain stable for a long time. Although W and W has been reported in several guidelines and recommendations it has never been validated, nor has it been specifically investigated. Furthermore it is not standardized. Therefore its application in clinical practice can differ in terms of tumor status assessment, type and timing of imaging or other exams utilized. In conclusion, while undertaking W and W to delay the first-line therapy by some weeks may be justified in good performance asymptomatic patients with low-grade NENs in order to usefully characterize the disease and patient and thereby choose the best therapy and therapeutic strategy, it seems to be far more difficult to justify W and W with the intent of avoiding an anti-tumor treatment. It should be considered that not only do NENs tend to grow even when they have very favorable biological characteristics but also that the alternative to W and W is most commonly a low toxic and effective treatment with somatostatin analogs.

Key words: Observation; Wait and see; *Watch and wait*; Surveillance; Neuroendocrine tumors

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Core tip: *Watch and wait* (W and W) is a term coined to indicate observation without therapy assessing the evolution of the tumor. Given that neuroendocrine tumors sometimes are radiologically stable over months since they tend to grow slowly observation has been reported as an option to be considered in several guidelines and recommendations. However it has neither validated nor specifically investigated so far. Therefore its application

in clinical practice is arbitrary and it differs in terms of tumor status assessment, type and timing of imaging or other exams utilized. While undertaking W and W to delay the first-line therapy by some weeks may be justified in good performance asymptomatic patients with low-grade neuroendocrine neoplasms (NENs) in order to usefully characterize the disease and patient and thereby choose the best therapy and therapeutic strategy, it seems to be far more difficult to justify W and W with the intent of avoiding an anti-tumor treatment. It should be considered that not only do NENs tend to grow even when they have very favorable biological characteristics but also that the alternative to W and W is most commonly a low toxic and effective treatment with somatostatin analogs.

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INTRODUCTION

Neuroendocrine neoplasms (NENs) represent a group of rare and heterogeneous malignancies, which can develop in various organ. They are classified on the basis of their level of aggressiveness into low, intermediate and high grades of malignancy.

Neuroendocrine neoplasms from the digestive tract, are classified on the basis of proliferation index as G1 ($\leq 2\%$ Ki-67), G2 (3%-20% Ki-67) and G3 ($> 20\%$ Ki-67). Furthermore, based on their morphology they are named "tumors" (NETs) when they are well differentiated, whereas "carcinomas" (NECs) when they are poorly differentiated^[1]. Neuroendocrine neoplasms from the thoracic region are classified into typical carcinoid, TC (< 2 mitoses/2 mm² with absence of necrosis), atypical carcinoid, AC (2-10 mitoses/2 mm² with necrosis), large cell neuroendocrine carcinoma, LCNEC (> 10 mitoses with extensive necrosis) and small cell lung cancer, SCLC (> 10 mitoses with extensive necrosis)^[2].

While high-grade NENs are treated with chemotherapy in the vast majority of cases when they are in advanced stage of disease, the therapeutic approach to advanced low-intermediate grade NENs varies. Somatostatin analogs (SSA), interferon (IFN), molecular targeted agents (MTAs), chemotherapy, peptide receptor radionuclide therapy (PRRT), and liver-directed treatments (LDTs), are all potentially effective therapies to propose, often in the same clinical setting. Although some of these therapies have been approved on the basis of positive regulatory phase III trials^[3-7] in specific settings and several guidelines about NENs do exist^[8,9], no sequencing or priority criteria about the different therapies have been validated. Furthermore, the clinical course of NETs is quite heterogeneous, with different spontaneous growth rates after diagnosis, and different

degrees of sensitivity to the same therapy even when they have similar characteristics.

"Watch and wait (W and W)", "watchful waiting", "wait and see", "observation" and "active surveillance" are all terms which are used to describe assessing the evolution of the tumor without an anti-tumor therapy. These terms have been applied synonymously to NETs as in rare cases they have a spontaneous very indolent clinical course. Sometimes they are also applied to a localized disease, as in the case of so-called pancreatic "incidentaloma", namely a < 2 cm isolated nodule in the pancreas. European Neuroendocrine Tumor Society (ENETS) 2016 guidelines recommend W and W for a < 2 cm pancreatic NET, "G1 or low G2, asymptomatic, mainly in the head, with no radiological signs suspicious for malignancy", and suggest that one also consider the patient's attitude, age and comorbidity. It is specified that the follow-up should be performed with endoscopic ultrasound (EUS), magnetic resonance imaging (MRI) (or computed tomography, CT) "every 6 to 12 mo". However, the length of follow-up is not specified^[10].

In the ENETS guidelines W and W is also recommended for advanced disease, for instance in NETs from the midgut when they are "non-functional, G1, low tumor burden, no symptoms, stable disease". This policy is advised even for pancreatic NETs, when they are "non-functional, G1, $\leq 10\%$ Ki-67, low tumor burden, stable disease or initial diagnosis, no symptoms"^[11].

In both midgut and pancreatic NETs the W and W policy is a possible alternative to SSA. However, SSA compared with placebo resulted effective in two phase III randomised controlled trials, with octreotide long-acting repeatable (LAR) producing a longer time to progression (TTP) in midgut NETs in the *PROMID* trial and lanreotide autogel significantly prolonging progression free survival (PFS) in enteropancreatic NETs in the *CLARINET* trial, respectively^[5,6]. Notably, time to progression (TTP) was quite short in the placebo arm of the *PROMID* trial demonstrating that also NETs with $< 3\%$ Ki-67, as were the vast majority of the tumors included in the *PROMID*, will progress eventually. Interestingly, NETs included in the *CLARINET* trial, which resulted as having a stable disease in 96% of cases in accordance with RECIST criteria, in fact were progressing at baseline, as showed with the so-called tumor growth rate (TGR)^[12].

Another report indicating that NETs tend to grow early spontaneously, is a retrospective analysis of more than 200 patients with advanced pancreatic NETs showing that those patients who did not receive antitumor treatment during follow-up had a significantly shorter PFS compared to treated patients, thus confirming that anti-tumor therapy can favorably impact on the clinical course of the disease^[13].

In the ENETS 2016 guidelines it is not specified whether radiological or functional imaging or both are recommended to monitor the tumor status of a low-grade NET; it is not clear whether some biochemical tests, such as chromogranin-A, should be performed periodically;

timing of follow-up imaging is not specified.

Furthermore no data exist about the impact of the W and W on the patient's quality of life and costs.

The W and W policy is debated also in other fields of oncology. For instance in renal cancer it was investigated in a phase II trial including medical anti-tumor treatment-naïve patients with advanced disease^[14]. The decision to choose W and W over immediate systemic therapy was made jointly by the patient and treating physician. Therefore patients underwent homogeneous radiological and clinical follow-up and also filled in quality of life questionnaires. Median time to radiological progression, RECIST-based, was 9.4 mo (95%CI: 7.4-13.4); at progression, patients received a first-line systemic therapy; no observed adverse effects on quality of life, anxiety and depression, were recorded during the observation period. Although this study seems to indicate that in some selected patients with metastatic renal carcinoma, active surveillance might be a good approach, homogeneous criteria for selection of patients to undergo W and W, type of follow-up and timing of first-line therapy remain debatable.

Further while in renal cancer one of the reasons for performing W and W instead of administering treatment to patients is to avoid therapies which may well be highly toxic, in NETs the choice is almost always between W and W and SSAs, which are a very low-toxic therapy.

Finally, in good-performance status asymptomatic patients with advanced NETs, the diagnostic work-up, morphological and functional staging and characterization of the disease require some weeks. Luckily in most cases this time without therapy is not detrimental for the patient and it allows an assessment to be made of clinical behavior and tumor growth, a thorough understanding of tumor and patient characteristics, and the discussion of the global therapeutic strategy within a dedicated multidisciplinary team. All of this may be very helpful to patients when compared with starting a single first-line therapy right from the time of diagnosis of an advanced NET. Proposing a W and W policy after completing this initial period of observation to a patient with a metastatic NET means waiting for a tumor growth or a clinical progression. On the one hand it is arbitrary to define whether morphological (radiological), functional (receptorial? metabolic?) or biochemical progression should be considered and with which threshold; on the other hand it could be detrimental to start therapy only when tumor-related symptoms arise. Nonetheless patients should be informed that no study has specifically investigated this topic comparing W and W and anti-tumor therapy, and therefore we have no evidence either for or against. Patients will need to understand that follow-up will be life-long even with stable disease, that there are data showing that the vast majority of advanced NETs tends to grow and that SSAs can be active even when the tumor is very indolent.

In conclusion, W and W policy in advanced NENs is

yet to be well-defined. First of all it should be clarified whether W and W means delaying or avoiding an anti-tumor treatment. Delaying may be justified in an asymptomatic good performance status patient with a low-grade NETs over some weeks in order to thoroughly characterize both disease and patient and so make a well-informed choice as to the best therapy and therapeutic strategy to pursue. This is a quite common clinical scenario in the field of NETs. By contrast it is hard to justify W and W with the intent to avoid treatment considering that low-grade advanced NETs tend to grow even when they have very favorable biological characteristics. Therefore, also in that case, rather than avoiding, it would mean once again delaying the first-line therapy. Of course the first-line therapy and the therapeutic strategy depend on the specific clinical context and on the goal of treatment. In other words in a patient who is a good candidate for a future absolute debulking, then the first-line treatment even more than an SSA should be applied even with a stable disease without any delay. On the other hand, in a patient with a metastatic low grade, really stable NET, when absolute debulking is not possible and the goal of the treatment is the tumor growth control over time with a systemic medical therapy, then a thoughtful analysis needs to be made. It is important to bear in mind the cost- and risk-benefit of SSA, which is the most commonly proposed therapy in such a context, and also the cost, invasiveness, impact on quality of life and possible detrimental effect of W and W.

I would argue that given the absence of evidence and of clinical trials designed to specifically investigate this topic, as is currently the case, clinicians should consider administering treatment to all patients, whether their NETs are advanced.

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