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Unmet Needs in Functional and Nonfunctional pancreatic neuroendocrine neoplasms(PanNENs)

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Abstract

Recently, European Neuroendocrine Tumor Society (ENETS)held working sessions composed of members of the advisory board and other Neuroendocrine neoplasm (NEN) experts to attempt to identify unmet needs in NENs in different locations or with advanced/poorly differentiated NENs. This section briefly summarizes the main proposed areas of unmet needs in patients with functional and non-functional pancreatic neuroendocrine neoplasms(PanNENs).

I. Introduction and general comments

Recently, European Neuroendocrine Tumor Society (ENETS) has held two working sessions on identifying unmet needs in a number of areas. There were 8 different working groups on neuroendocrine neoplasms (NENs) in different locations [pulmonary,

gastroduodenal, Jejunal/ileal, PanNEN, colorectal, appendiceal], as well as with different classifications [High grade NEN] and a separate group dealing with advanced disease. A primary purpose of these working groups was to identify possible future protocol topics. This report summarizes a number of aspects from the working group dealing with Functional PanNENs(F-PanNENs) and Nonfunctional PanNENs (NF-PanNENs). Although many of the unmet needs in patients with PanNENs relate to treatment/management of advanced disease or the specific treatment of patients with high grade tumors (G3NET/G3NEC), because these are considered in specific, separate sessions, overlap with this area was generally limited in our considerations of unmet needs and thus we are dealing with primarily well differentiated pancreatic neuroendocrine tumors(PanNENs).

PanNENs comprise 7% of all pancreatic neoplasms with an age adjusted incidence of 0.52/100,000(2004-2012), whereas pancreatic adenocarcinomas have an incidence during this time of 7.34/100,000[1]. Similar to other NENs, the incidence of PanNENs is increasing[1-3]. Compared to pancreatic adenocarcinomas, patients with PanNENs present at an earlier age (61 vs 69 yrs.), at diagnosis there is a higher percentage in an early stage (stage 1, 20.5% vs 6%), and have a higher 5-yr disease-specific survival (51.3 vs 5%)[1].

Patients with F-PanNENs comprise 9.2% of all patients with PanNENs in the National Cancer Institute's SEER database[2], however they present a number of specific management problems, because except for insulinomas, many present with advanced disease and cannot be surgically cured[1;2;4]. Therefore, both the hormone-excess state and the growth of the tumor itself need to be dealt with, often separately[5-8]. F-PanNENs include insulinomas>gastrinomas> vasoactive intestinal peptide secreting NENs (VIPomas)>somatostatinomas, Growth Hormone Releasing factor secreting NENs (GRFomas), Adrenocorticotropic hormone secreting NENs (ACTHomas), Parathyroid Hormone related peptide secreting NENs (PTH-RPomas), PanNENs with carcinoid syndrome or hypercalcemia> other very rare F-PanNENs (PanNEN secreting luteinizing hormone, erythropoietin, Glucagon-like peptide 1 or 2 secreting NEN (GLP1/2), etc.)[7].

The percentage of PanNENs in different series of NEN patients varies considerably. In the SEER database PanNENs comprised <10% of all NEN patients[9]; however in the recent ENETS database consisting of >12,000 NEN patients, PanNEN patients comprised 26% of all patients[10].

The treatment/management of PanNENs is further complicated by the fact that up to 10% can be part of a hereditary syndrome[5;11]. In patients with Multiple Endocrine Neoplasia-type 1(MEN1), 90-100% of patients have NF-PanNENs, which are symptomatic [due to nonhormonal symptoms] in 0-12%, with most having only small, microscopic tumors: 20-80% have a F-PanNEN with 20-60% developing Zollinger-Ellison syndrome(ZES), 17-31% having insulinomas and <3-4% other F-PanNENs[11;12]. PanNENs occur in 10-17% of patients with von Hippel Lindau Disease(VHL)(>98% NF-PanNEN), 0-10 % of patients with Neurofibromatosis 1 and rarely in patients with tuberous sclerosis[11]. In various series 20-25% of all Zollinger-Ellison patients have MEN1, whereas <3% of patients with insulinomas have MEN1[11]. The presence of the hereditary syndrome is important to recognize because these patients have additional features requiring treatment including genetic screening, and different management of the PanNEN, because they may be multiple, not easily curable and they frequently pursue an indolent course in many patients[11-14].

For most patients surgical resection remains the only treatment modality that can cure patients with PanNENs, thus it is recommended for all patients with potentially resectable disease without a medical complication that increases the surgical risk to prohibitive levels[5;8]. Unfortunately, many patients with advanced disease (particular Stage IV) have unresectable disease due to diffuse or distant metastases[5;8].

In the SEER database which includes patients with malignant disease, 14%, 23% and 54% of patients with PanNENs have localized, regional or distant disease with median survivals of 124 mos., 70 mos. and 23 mos.[15].

II. Unmet needs. PanNENs (Table 1). General comments

Unmet needs in patients with PanNENs [not related to treatment/management of advanced or Grade 3(G3) disease] can be identified in many areas and some of these are listed in Table 1.

A particularly important problem that includes a number of unmet needs is the availability of a liquid tumor marker that will allow earlier diagnosis; that will have prognostic value for progression/aggressiveness and which can predict early recurrence after surgery. While the development of the ENETS, World Health Organization (WHO)

and other classification systems, as well as the grading system (G1, G2, G3NET, G3NEC(neuroendocrine carcinoma),) has been a very important advance with established prognostic value[16-18], there still is great variation in the behavior of individual patients with a given tumor category. Furthermore, available tumor markers which can be assessed in blood, etc. which are current approved, do not have the sensitivity or specificity to detect small NF-PanNENs in most cases. Furthermore, they are generally not helpful for predicting recurrence or progression of a PanNEN in most patients. While there are a number of liquid tumor markers that show promise (NETEST, circulating tumor DNA assessment, etc.) at present, they are not approved for routine use[19].

A second important unmet need in PanNEN patients, which will be discussed in more detail below, relates to the recent widespread change in the approach to patients with small (≤2 cm) sporadic, asymptomatic NF-PanNENs (Table 1). Increasingly, patients with small (≤2 cm), asymptomatic, NF-PanNENs are not being operated on, and instead, a watch and wait approach is being increasingly used [20-23]. This approach has raised a number of queries such as how to properly follow these patients, what imaging studies to use and what are the best criteria to determine the need for surgery or watch and wait[19-23].

A third area of unmet need in patients with PanNENs, especially with NF-PanNENs, is the need post resection, to identify which patients are likely to develop early recurrence or aggressive tumors and therefore require more frequent and extensive re-evaluations, as opposed to patients which are likely cured long-term and require less frequent or extensive postoperative follow-up (Table 1). Scoring systems have been proposed to identify patients at higher risk of recurrence, and other prognostic variables proposed in other studies to identify patients with increased risk of recurrence, however they have not been prospective evaluated[24-31].This also relates to identifying the group of higher risk patients who might benefit by adjuvant treatments[32]. The recurrence rate after resection in patients with NF-PanNENs varies from 9-40% at 3 years and is affected by whether patients with hereditable PanNENs are included, the percentage of patients with higher grade tumors(G2, G3) included, the percentage of patients with tumors with invasion (vascular, neural, lymphatic), disease stage and percentage of patients with larger tumors (>2-3 cm) [20;21;25;33-36]. This will be dealt with in more detail below.

A fourth area of unmet need in patients with F-PanNENs is the need for improved methods to control the hormone excess state in patient's refractory to somatostatin analogues or other current therapies[6]. This is particularly true of patients with metastatic insulinomas, VIPomas, rare patients with other F-PanNENs, and patients with carcinoid syndrome, which can uncommonly be due to a PanNEN[6;7]. This is rarely a problem now in patients with Zollinger-Ellison syndrome (ZES), because the acid hypersecretion can be controlled in all patients who can take oral medications, with PPIs or histamine H2 receptor antagonists[37-39]. This will be briefly dealt with in more detail below.

A fifth area of unmet needs occurs in the management of patients with hereditable PanNEN syndromes (Table 1). This includes primarily patients with MEN1 or VHL and rare patients with neurofibromatosis 1 or tuberous sclerosis[5;11] with small NF-PanNENs or gastrinomas which are not easily curable, are often indolent, however in up to 15% can be aggressive and lead to early mortality[11;40-43]. This will be dealt with in more detail below.

A sixth area relates to treatment of patients with advanced locally invasive disease due to an aggressive PanNEN, either potentially resectable or thought unresectable (Table 1). In the locally advanced disease possibly resectable the definition of prognostic factors as well as the role of possible additional antitumor therapies post resection (adjuvant therapy) are important unanswered queries. In patients with locally advanced unresectable disease, whether aggressive/debulking surgery prior to other anti-tumor therapies, or after an attempt at tumor downsizing with neoadjuvant therapy such as peptide radioreceptor therapy (PRRT), chemotherapy or other medical treatment is, in general, unclear in these patients, as are predictive factors for success. This will be dealt with in more detail below.

III. Unmet needs. Potential specific protocol topics (Table 2)

General points

At the initial meeting of the ENETS working group (Group IV) dealing with unmet needs in PanNEN patients (not including advanced or G3 disease), 6 different possible protocol topics were considered which integrated a number of the unmet needs reviewed above (Table 2). These areas were briefly reviewed in Table 1 and in the previous section, but will be discussed in more detail here.

<u>Possible Unmet Need protocol #1:</u> Growth of sporadic NF-PanNENs ≤ 2cm that plan to follow? (Table 2)

It is a well-established recommendation in ENETS/NANETS and other guidelines that in patients with small, asymptomatic NF-PanNENs (≤2cm) with hereditary PanNEN syndromes, the standard approach is not to surgically resect the tumor but to carefully watch/wait [5;12;44]. This recommendation is based on the findings that NF-PanNENs of this size are not associated with increased mortality in MEN1 patients, many do not grow or show aggressive behavior, and these patients cannot be completely cured of PanNENs, because they all have small, microscopic NF-PanNEN tumors throughout the gland and only 0-12% ever become symptomatic[5;11;12;45-47]. Only recently is this approach being increasingly used in patients with sporadic, asymptomatic NF-PanNENs[19-21;23;48]. This recommendation is not without controversy with some authors advocating surgery for all PanNENs, whereas others support the conclusion that small, asymptomatic PanNENs are good candidates for surveillance[19-21;49-52].

At present there are limited tools which identify which of the small, asymptomatic PanNENs will grow; and therefore, the approach generally used is to serial image this tumor[19-21;49-51]. There also is not complete agreement on what imaging modality should be used. Whereas endoscopic ultrasound (EUS) is the most sensitive for detecting small PanNENs and is frequently advocated for use in hereditary PanNEN patients such as those with MEN1[47], it requires expertise, is available in only some centers and is an invasive procedure, however it has the advantage of allowing directed biopsies/cytology to be performed. A recent study reports that EUS consistently overestimated the size of PanNENs≤2cm, whereas assessment by Magnetic Resonance Imaging (MRI) most accurately determined the lesion size found at surgery[53].

In Table 2 with this proposed protocol (#1) are listed various pathologic, radiologic, liquid tumor markers and demographic features that have been reported in numerous studies to have prognostic significant in PanNENs that could be incorporated into this study. The prognostic pathologic features included here are discussed in more detail in proposed protocol #2 below. Recent studies report that a number of radiologic parameters can have predictive value for tumor aggressiveness and correlate to varying degrees with

the pathologic grading[48]. These include the correlation of grading/tumor aggressiveness with ^{18}F-Fluorodeoxyglucose (FDG) PET/CT positivity, the ^{18}F-FDG maximum standardized uptake (SUV/MAX) value, as well as the diffusion weighted MRI- apparent diffusion coefficient values[48;54-57]. Recent studies report that the Ki67 value correlates significantly with the size of the PanNEN[58;59], thus this should be studied prospectively in more detail.

Possible unmet need protocol #2: Investigate prognostic factors for progression/aggressiveness /recurrence of PanNENs (primarily post resection) (Table 2)

Even though the WHO/ENETS Classification and particularly the grading of PanNENs, has been shown in most studies to be a strong prognosticator of biologic behavior/survival [16;60], for a given PanNEN the biologic behavior within one grade can be very variable and not predictive[59] This is particularly important in patients post resection of PanNENs, because if reliable predictors of recurrence/growth/aggressive behavior were available, the postoperative follow-up time/investigations could be adjusted and appropriate neoadjuvant treatments considered[32]. Recurrence rate post resection in patients with PanNENs varies markedly in different series and, as outlined in a previous paragraph. it is affected by the type of PanNEN included (insulinomas, the most frequent F-PanNEN, have a very low recurrence rate)[61]; the tumor grade; the tumor stage; and the pathologic features other than grade/differentiation of the tumors such as degree of invasion[20;21;24-31;33-36]. In addition other molecular features of PanNENs have been shown to correlate with tumor aggressiveness/recurrence including ATRX/DAXX/telomere changes and changes in other chromatin remodeling genes[62], miRNA/mRNA transcriptosome profiles[63] methylation status [64] and a number of other alterations[65](Table 2). Each of the radiologic features discussed in possible unmet needs project #1 above could also be correlated with tumor aggressiveness/recurrence either from preoperative studies/pretreatment studies or residual tumor.

<u>Possible unmet need protocol #3:</u> Potentially resectable locally advanced PanNEN. Prospectively assess prognostic factors to predict postop course, potential need for additional treatments early (Table 2)

A proportion of patients with PanNENs present with locally advanced disease which is thought resectable but may require extensive surgery[66-74]. There are a number of unmet needs in the treatment of these patients. A number of potential prognostic factors have been described including tumor grade, extent of histological invasion, vessel/neural invasion, the presence of concomitant liver metastases, and tumor stage, however these have not been examined in prospective studies[66;67]. In general, the treatment approach to these patients has not been systematic studied [66;67;74]. Not only are predictive factors not clearly established, but the question of adjuvant, or even neoadjuvant treatment in these patients is not resolved. In a study of such patients the various pathologic, radiologic, liquid tumor markers and demographic features that have been reported in numerous studies to have prognostic significant in PanNENs could be incorporated (Table 2).

<u>Possible unmet need protocol #4:</u> Growth of MEN1 NF-PanNENs< 2cm that plan to follow? (Table 2)

It is important to establish whether a patient presenting with either a NF-PanNEN or F-PanNEN has it as part of an inherited syndrome, particularly, MEN1 or VHL[5;11;39]. A high degree of suspicion is needed because patients with inherited PanNEN syndromes can present with symptoms due to the PanNEN and not be easily be distinguished from the sporadic cases (this is particularly true of patients with MEN1, particularly MEN1/ZES)[11;75;76]. The management of PanNENs in patients with inherited PanNEN syndromes, particularly MEN1, and to a lesser extent, VHL, continues to remain controversial [5;11;12;47;77;78]. This includes controversy both in the management of NF-PanNENs in these patients, as well as some F-PanNENs such as gastrinomas[5;11;12;47;77;78]. All agree that patients with nongastrinoma, such as with F-PanNENs such as insulinomas, glucagonomas, GRFomas, etc., as well as patients with larger NF-PanNENs (>2-3cm) or with a symptomatic NF-PanNEN, should undergo surgery and they have a high likelihood of success[5;11;12;44;47]. The controversy primarily involves in MEN1 patients, the treatment of small (≤2 cm), asymptomatic NF-

PanNENs as well as the treatment of patients with ZES with small lesions(≤2cm) [5;11-13;44;47]. At present most guidelines (ENETS, NANETS) recommend that MEN1 patients with small NF-PanNENs (≤2cm). which are almost invariably asymptomatic, should be treated with a watch and wait policy[5;12;44;47]. This policy evolved from the findings that these small NF-PanNENs were not associated with increased mortality, the NF-PanNENs are multiple, that the patient cannot be cured of all NF-PanNEN lesions without a total pancreatectomy, and that most of these when followed show minimal growth[5;11;12;79-81]. In the case of ZES in MEN1 patients a similar problem exists as the gastrinomas are in the duodenum in 80-90% of cases, they are invariable multiple, 50-70% are associated with local lymph node metastases, not curable without aggressive selection such as a Whipple resection; and long-term studies show unoperated patients with <2-3cm imageable lesion have an excellent long-term survival, so it is generally recommend that this group also not undergo routine resection[11-14;47;82;83]. Controversies exist because the natural history of the small PanNEN is not well defined, the imaging approaches to follow these patients are not agreed on, the place of EUS is not resolved, and the place of molecular imaging with ^{68}Ga-DOTATATE or ^{18}F-FDG-PET/CT is not defined, hence all require study and thus they are a major unmet need in these patients with hereditable NEN syndromes[5;11;12;41;47]. In a study of such patients the various pathologic, radiologic, liquid tumor markers and demographic features that have been reported in numerous studies to have prognostic significant in PanNENs could be incorporated (Table 2).

Possible unmet need protocol #5: Unresectible locally advanced PanNEN. Best Treatment? (Table 2)

A proportion of patients with PanNENs present with locally advanced disease which is thought unresectable and the treatment options with these patients are unclear[66-68;70;84]. In general, the treatment approach to these patients has not been systematic studied. There are a few reports of aggressive surgical treatment of this group of patients [66;67;69;70]. Also, there are reports of attempts at downsizing the invasive PanNEN with various neoadjuvant agents including everolimus, PRRT, and chemotherapy[71;72;84-88;88-94], however predictive factors for success are unknown and the course after such an approach has not been well studied. The recent approval of PRRT and its increasing

availability may be particularly useful for this approach. In a recent study [88] involving patients with advanced PanNENs, PRRT with ^{177}Lu Octreotate resulted in 9 patients downsized to the extent that successful surgery could be performed. In a future study of such patients the various pathologic, radiologic, liquid tumor markers and demographic features that have been reported in numerous studies to have prognostic significant in PanNENs could be incorporated (Table 2).

Possible unmet need protocol #6; Patients with advanced or uncontrolled F-PanNENs (except gastrinoma) (Table 2).

Unfortunately, patients with F-PanNENs frequently present with liver metastases and extensive disease, with >50% of all, except insulinomas (5-10%), showing malignant behavior with hepatic metastases in most studies[5;38;39;95]. Because of this extent of metastatic disease, a large percentage of these patients are not surgically curable[5;38;39;95]. Hence, the hormone excess state must be treated medically. Although somatostatin analogues, and other specific drug treatments have been effective in many patients, a proportion develop refractory disease[6;96]. This is particularly true for patients with metastatic insulinomas, VIPomas, ACTHomas, PTHrPomas and carcinoid syndrome (a small percentage which are due to PanNENs)[6;7;96]. Whereas, a number of new approaches show promise, particularly the use of PRRT and everolimus, these have generally only been reported in small series [7]. The result is that no predictive factors for response have been clearly defined, the long-term results and recurrence rate are unclear, the possibility of retreatment yielding additional responses is undefined, and the role of these agents combined with other antisecretory agents is unclear and thus there are a number of unmet needs in the possible treatment of these refractory F-PanNENs.

IV. Conclusions:

There are a number of unmet needs in the management of patients with F-PanNENs and NF-PanNENs which are briefly reviewed here, which could be examined and possibly resolved in future studies. Possible resolution of a number of these unmet needs is now possible because of recent advances. These include: the formation of ENETS specialty centers which concentrate NEN/PanNEN patients in centers and increase the possibility of multicenter studies; the development of classification/grading systems

with strong predictive value; the increasing understanding of molecular factors response for aggressive behavior or having prognostic value; the increasing definition of imaging parameters that correlate with aggressiveness/tumor behavior; the development of possible predictive liquid biopsies (circulating tumor DNA assessment, NETest, etc.); and the available of new effective anti-tumor treatments such as PRRT and molecular targeting agents.

Table 1: Some unmet needs in patients with PanNENs (excluding issues dealing with advanced disease)

A. **Related to early diagnosis**:
- improved liquid biomarkers to identify patients with early PanNENs
- sensitive imaging modalities

B. **Related to Prognosis**:
- improved prognostic liquid biomarkers
- improved prognostic biomarkers-tissue related
- Better definition of which patients need resection, and which patients can be followed (NF-PanNEN, MEN1, VHL, MEN1/ZES)
- Imaging modalities/parameters which have enhanced prognostic value

C. **Related to Progression/aggressiveness**:
- improved liquid biomarkers
- improved biomarkers-tissue related
- Imaging modalities/parameters which allow early detection

D. Related to detection of early recurrence post resection
- improved liquid biomarkers
- improved biomarkers-tissue related
- Imaging modalities/parameters which allow early detection

E. Adjuvant treatments to delay/prevent recurrence

F. Enhanced methods to control the hormone excess state in patients with refractory F-PanNENs

G. Patients with inherited NEN syndromes (particularly MEN1)
1. Define natural history of different NENs
2. Establish criteria predictive of small PanNENs behavior? treat/watch
3. Establish natural history of NF-PanNENs post resection

H. Define which patients with advanced locally invasive disease thought unresectable would benefit from neoadjuvant treatment? regimen

I. Define prognostic factors and need for additional anti-tumor treatments in patients with locally advanced PanNENs

Table 2: Outline of proposals for possible protocols of unmet needs in patients with F-PanNENs and NF-PanNENs

1. Growth of sporadic NF-PanNENs ≤ 2cm that plan to follow?

a. Natural history- Follow-EUS/? MRI
b. Pathology-Histologic features-vascular/neural invasion, etc./possible molecular factors (ATRX/DAXX/telomere changes/Ki67/Ras/p53 /RB/ etc./ next generation or whole genome exon sequencing?
c. Radiology. 68Ga-DOTA-PET/CT /Diffusion weighted MRI- SUV/MAX value / 18F-FDG PET/CT positivity and SUV/MAX value
d. Tumor markers (CgA, NET blood transcript analysis
e. Demographic or surgical /path features (Ln positivity, Ln ratio, demographic features, growth prior to study/surgery/etc.)

2. Investigate prognostic factors for progression/aggressiveness /recurrence of PanNENs (primarily post resection) (particularly G2)

a. Pathology-Histologic features-vascular/neural invasion, etc./possible molecular factors (ATRX/DAXX/telomere changes/Ki67/Ras/p53 /RB/ etc./ next generation or whole genome exon sequencing?
b. Radiology. 68Ga-DOTA-PET/CT /Diffusion weighted MRI- SUV/MAX value / 18F-FDG PET/CT positivity and SUV/MAX value
c. Tumor markers (CgA, NET blood transcript analysis
d. Demographic or surgical /path features (Ln positivity, Ln ratio, demographic features, growth prior to study/surgery/etc.)

3. Potentially resectable locally advanced PanNEN. Prospectively assess prognostic factors to predict postop course, potential need for additional treatments early

a. Pathology-Histologic features-vascular/neural invasion, etc./possible molecular factors (ATRX/DAXX/telomere changes/Ki67/Ras/p53 /RB/ etc./ next generation or whole genome exon sequencing?
b. Radiology. 68Ga-DOTA-PET/CT /Diffusion weighted MRI- SUV/MAX value / 18F-FDG PET/CT positivity and SUV/MAX value
c. Tumor markers (CgA, NET blood transcript analysis
d. Demographic or surgical /path features (Ln positivity, Ln ratio, demographic features, growth prior to study/surgery/etc.)

4. Growth of MEN1 NF-PanNENs √ 2cm that plan to follow?

a. Natural history- Follow-EUS/? MRI
b. Pathology-Histologic features-vascular/neural invasion, etc./possible molecular factors (ATRX/DAXX/telomere changes/Ki67/Ras/p53 /RB/ etc./ next generation or whole genome exon sequencing?
c. Radiology. 68Ga-DOTA-PET/CT /Diffusion weighted MRI- SUV/MAX value / 18F-FDG PET/CT positivity and SUV/MAX value
d. Tumor markers (CgA, NET blood transcript analysis
e. Demographic or surgical /path features (Ln positivity, Ln ratio, demographic features, growth prior to study/surgery/etc.)

5. Unresectible locally advanced PanNEN. Best Treatment?

a. Is there a role for neoadjuvant treatments (downsizing either with PRRT or chemotherapy vs medical Tx)?
b. Should ± surgical debunking be done with postop PRRT
c. Should various radiological assessments (68Ga-Dota results/18F-FDG be used to select patients for surgery?

6. Patients with advanced or uncontrolled F-PanNENs (except gastrinoma)

a. Treat with PRRT vs SS analogue to see if can control functional state with reduced or no SS analogue
b. What predictors of response of SS analogue resistance cases to PRRT? Everolimus?

Abbreviations: EUS-Endoscopic ultrasound; MRI-magnetic resonance imaging; RB-retinoblastoma gene/protein; CgA-chromogranin A; SUV- standardized uptake value; Ln-lymph node; Tx-treatment, SS-somatostatin; postop-postoperative; FDG-fluorodeoxyglucose; PRRT-peptide radioreceptor therapy; path-pathology

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