Treatment of Intestinal NETs (Including Appendix)

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15.1 Introduction

The treatment of intestinal neuroendocrine tumors (NETs) remains a challenge for physicians, requiring a multidisciplinary approach and a tailored patient's evaluation [1]. Prognosis of this disease depends on a number of factors, including specific primary tumor site, tumor grade (expressed as Ki67 value), staging, and expression of somatostatin receptors (sstr). Among these factors, grading is widely considered the most powerful, with significant role in terms of predicting tumor behavior and patients' prognosis. The recent WHO 2019 classification identifies four different categories, based on Ki67 values and tumor differentiation [2]: NET G1, well-differentiated morphology and Ki67 < 3%; NET G2, well-differentiated morphology and Ki67 3–20%; NET G3, well-differentiated morphology and Ki67 > 20%; NEC G3, poorly differentiated morphology and Ki67 > 20%. The majority of intestinal NETs are included in NET G1 to NET G2 groups, whereas NET G3 and NEC are considered rare entities. Tumor spontaneous behavior, response to treatments, and thus patient's clinical outcome strictly depend on grading. In fact, in some cases, intestinal NETs may present as indolent, slow-growing diseases, whereas in other cases, tumor may be more aggressive resulting in a worse clinical outcome. From a clinical point of view, intestinal NETs may be divided into two major categories: "functioning tumors" when a specific clinical syndrome (usually a carcinoid syndrome, mainly characterized by diarrhea and flushing, with cardiovascular disease and difficult to breath in advanced stage) related to secretion of active substances by the tumor exists; otherwise, the tumor is defined as "non-functioning" when only generic mass-related symptoms are present.

Irrespective of the tumor functionality, intestinal NETs are commonly diagnosed at advanced stage, with distant metastases which are most frequently found in up to 75% of patients [3, 4]. Nevertheless, long-term survival rates are fairly good, ranging from 45% to 75% depending on the above-mentioned prognostic factors [4–6] and the efficacy of therapeutic management.

Current scientific evidences demonstrate a range of efficient therapies to treat advanced intestinal NETs, including somatostatin analogs (SSAs), targeted therapy, peptide-receptor radionuclide therapy (PRRT) (Table 15.1, Fig. 15.1) which, in addition to surgery and liver-directed ablative treatments, need to be carefully considered when approaching the therapeutic sequence of these patients.

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Table 15.1 Randomized-controlled trials performed in advanced NENs over time

Reference	Number of patients evaluated	Drug used	Main finding
Arnold et al. CGH 2005 [7]	105 gastrointestinal and pancreatic	Octreotide vs. octreotide + interferon	Combination treatment was not superior to monotherapy concerning progression-free and long-term survival
Yao et al. JCO 2017 [8] (SWOG study)	427 gastrointestinal	Octreotide + interferon vs. octreotide + bevacizumab	No significant differences in PFS were observed between the bevacizumab and IFN arms
Faiss et al. JCO 2003 [9]	80 gastrointestinal and pancreatic	Lanreotide vs. interferon vs. lanreotide + interferon	Comparable antiproliferative effects among the three arms
Kolby Br J Surg 2003 [10]	68 midgut carcinoids	Octreotide alone vs. octreotide plus interferon	Addition of IFN-α to octreotide may retard tumor growth in patients with midgut carcinoid tumors
Rinke et al. JCO 2009 [11] (Promid study)	85 midgut carcinoids	Octreotide vs. placebo	Octreotide LAR significantly lengthens time to tumor progression compared with placebo
Caplin et al. NEJM 2014 [12] (Clarinet study)	73 midgut (total)	Lanreotide 120 mg vs. placebo	Lanreotide was associated with significantly prolonged progression-free survival among patients with metastatic gastroenteropancreatic neuroendocrine tumors of grade 1 or 2
Strosberg et al. NEJM 2017 [17] (Netter-1 study)	229 midgut carcinoids	[177Lu]Lu-DOTA-TATE vs. high dose octreotide	^{177}Lu-Dotatate resulted in markedly longer progression-free survival
Pavel et al. Lancet 2011 [24] (Radiant-2 study)	224 small intestine	Octreotide + everolimus vs. octreotide + placebo	Everolimus plus octreotide LAR, compared with placebo plus octreotide LAR, improved progression-free survival in patients with advanced neuroendocrine tumours associated with carcinoid syndrome
Yao et al. Lancet 2016 [25] (Radiant-4 study)	302 gastrointestinal or lung	Everolimus vs. placebo	Everolimus was associated with significant improvement in progression-free survival

For each study, the number of enrolled patients, the therapeutic schedule, and the main finding are reported. Further data may be found in the text

15.2 Medical Treatment for Advanced Disease

15.2.1 Somatostatin Analogs

Synthetic somatostatin analogs octreotide and lanreotide are widely considered the first-line therapy for patients with well-differentiated G1 and G2 intestinal NETs. Up to 90% of NETs carry sstr on tumor cell membrane and are therefore optimal candidate to receive SSAs-based therapy. Since their introduction in the early 1980s, they showed a clear activity to improve diarrhea and flushing in patients with carcinoid syndrome, as well as to decrease tumor markers chromogranin A and urinary 5-HIAA, by inhibiting the release of neuropeptide. In the following years, several retrospective and phase 2 trials proposed their ability to reduce tumor growth in patients with well-differentiated NETs. The antiproliferative activity of octreotide was definitively demonstrated in 2009, when the phase 3 PROMID trial was published [11]. In that trial, a clear benefit in terms of progression-free survival (PFS) was observed in patients with advanced "midgut carcinoid" (mainly small intestine NETs) receiving octreotide LAR 30 mg every 4 weeks, compared with placebo, with a 66% reduction in risk of disease progression. This figure was confirmed and further corroborated in the CLARINET study [12], the largest phase 3 trial ever published on SSAs and NETs, including 204

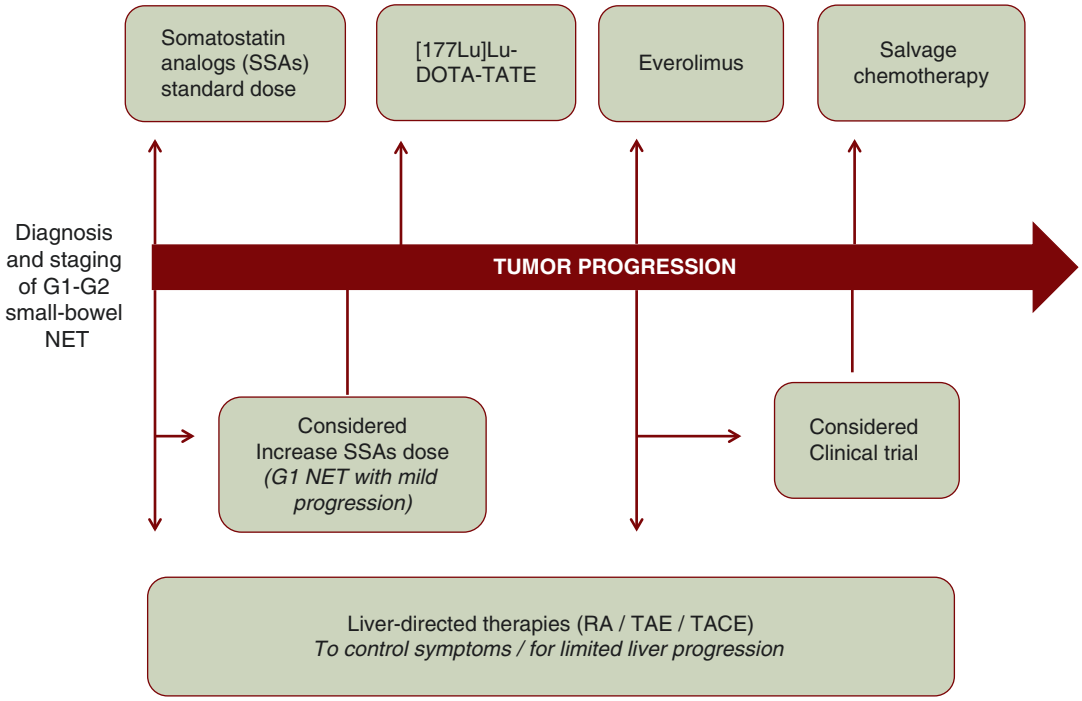

Fig. 15.1 Proposed therapeutic algorithm for the treatment of unresectable well-differentiated G1–G2 small-bowel NET

patients with advanced well-differentiated NETs rising from gastrointestinal tract or pancreas. Lanreotide extended-release (autogel) at a dose of 120 mg every 4 weeks significantly decrease the risk of tumor progression compared with placebo (−53%), even in those tumors with relatively high proliferation (NET G2 with Ki67 < 10%) or presenting metastatic liver involvement >25%. Both trials showed an excellent safety profile in patients receiving SSAs, most frequent serious adverse events (AEs) being diarrhea, abdominal pain, cholelithiasis, and flatulence.

Given the findings reported by those phase 3 trials, octreotide LAR 30 mg/4 weeks and lanreotide extended release (autogel) 120 mg/4 weeks are recommended by international guidelines as first-line therapy for well-differentiated, slow-growing NET G1 and G2 gastro-entero-pancreatic NETs expressing sstr [13, 14].

Meanwhile, several studies have suggested that an escalation of SSAs dosage might provide additional antiproliferative activity compared with the above-mentioned standard doses. Higher doses of SSAs, also referred to as non-conventional SSA doses, are achieved by either increasing administered dose (increased dose intensity; e.g., octreotide LAR 60 mg) or reducing interval between administrations (increased dose density; e.g., lanreotide autogel 120 mg every 21 or 14 days). Above-label doses of SSAs are being used frequently for the management of NETs in clinical practice in patients with disease progression or uncontrolled symptoms while on standard dose therapy without excessing toxicity [15, 16]. However, solid data regarding the role of non-conventional SSA doses are lacking, given the absence of large, prospective trials focusing on this topic. To date, increasing SSA dose above the standard may be proposed in selected NET patients progressing with the standard SSA dose after a multidisciplinary discussion has been made, carefully considering the kind of tumor progression (increase in number of lesions and/or increase in tumor size), presence of uncontrolled NET-related syndrome, patient's

age and comorbidities, and potential therapeutic alternatives including PRRT and everolimus-based target therapy.

Clinical trial with lanreotide high doses has recently been completed, and data will be published shortly (https://clinicaltrials.gov/ct2/show/NCT02651987).

15.2.2 Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) is the result of a combination of a radionuclide and a peptide conjugate with an appropriate chelator that specifically binds to sstr delivering a cytotoxic radiation to the tumor. Upon binding of the radiolabeled peptide to the receptor, after an internalization of the compound has took place, the emission of ionizing radiation from the bound radionuclide occurs, inducing selective tumor cell destroy. In clinical practice, this model of radio-labeled targeted therapy consists of [177Lu]Lu-DOTA-TATE, a complex compound in which 177Lutethium is conjugated with a chelator (DOTA) and a targeting peptide (octreotate).

After almost 20 years during which several non-randomized studies, often retrospective, proposed this treatment to be effective in different kinds of NETs, the first phase 3 randomized trial NETTER-1 definitively confirmed the clear benefits of [177Lu]Lu-DOTA-TATE in advanced, progressive intestinal NETs [17]. In that trial, 229 patients were randomized to receive [177Lu]Lu-DOTA-TATE or high-dose octreotide (60 mg/4 weeks); the risk of tumor progression or death was reduced in the active arm by 79%, and an objective tumor response in terms of significant reduction in tumor size was observed in 18% of patients. The treatment was well-tolerated, with most important AEs being lymphopenia, vomiting, diarrhea, nausea, and abdominal pain. Given the impressive results obtained by the NETTER-1 trial, [177Lu]Lu-DOTA-TATE has been approved by international regulatory agencies FDA and EMA for treating patients with advanced, progressive gastrointestinal or pancreatic, well-differentiated G1 and G2 NETs expressing somatostatin receptors. A number of publications outside the regulatory trial further corroborates data from NETTER-1 study. In fact, similar findings were reported by a very large retrospective study including a mixed population of 1214 patients with NETs from different sites treated with [177Lu]Lu-DOTA-TATE over 15 years period of time [18]. The reported median overall survival rate was 58 months in the subgroup of patients with intestinal NETs and documented progressive disease, a promising figure if compared with data deriving from other therapeutic strategies. Again, a significant ability to induce objective tumor response was reported in 30% of patients. Safety data analyses were in agreement with those reported by the phase 3 trial. While [177Lu]Lu-DOTA-TATE PRRT is considered a well-tolerated therapy with few, usually transient, AEs, some concerns have been raised concerning long-term toxicity. The risk of persistent renal toxicity has significantly decreased over time after specific administration protocols including kidney protection with amino acids infusion has been applied [18, 19]. As far as hematological toxicity is concerned, myelodysplastic syndrome and acute leukemia have been reported to rarely occur in the late follow-up of patients treated with PRRT. Although severe, these conditions represent very rare event, being reported in nearly 1% of patients, particularly in those previously treated with alkylating agents [19, 20]. This observation further highlights the need to properly plan the optimal therapeutic sequence in NET patients, to provide optimal anti-tumor activity and to avoid unnecessary toxicity.

Tumor size is considered a prognostic factor for patients treated with [177Lu]Lu-DOTA-TATE, and an inverse correlation between tumor burden and treatment effectiveness has been proposed in the past. However, a recent sub-analysis from the NETTER-1 trial showed clear [177Lu]Lu-DOTA-TATE activity regardless of baseline liver tumor burden and presence of large target lesions [21].

Beyond efficacy, [177Lu]Lu-DOTA-TATE PRRT has showed to have a positive impact on

patients' quality of life (QoL), by prolonging global health time to QoL deterioration, as well as by improving both physical and role functioning in treated patients [22]. Maintaining QoL is particularly important in patients with NETs, given the relatively indolent course of these diseases which gives patients the possibility to receive several therapies during the long clinical course.

Furthermore, there is a promising emerging evidence supporting the effectiveness of PRRT in somatostatin-receptor imaging (SRI)-positive G3 disease. In fact, favorable clinical outcome, in terms of both disease control rate (69–78%) and median PFS (11–16 months) have been also observed in patients with highly proliferating G3 tumors with Ki67 ranging between 20% and 55% [23], thus suggesting that PRRT might play a significant role in the therapeutic sequence also in this more aggressive setting of disease.

Although placing [177Lu]Lu-DOTA-TATE PRRT in the therapeutic sequence of intestinal NETs still remains an interesting open question which need to be definitively answered, it is reasonable to consider this treatment as second-line therapy after failure of SSAs.

15.2.3 Everolimus

Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR) used as a systemic therapy in lung and gastroenteropancreatic neuroendocrine tumors at a dose of 10 mg/day. In the last decade, its activity in different settings of NETs has been extensively investigated. Concerning intestinal NETs, two phase 3 RCTs have focused on the activity of this compound in this subgroup of NET. The Radiant-2 trial [24] enrolled 429 patients with advanced progressive gastrointestinal NET with previous history of carcinoid syndrome; although it failed to reach the pre-specified statistical significance threshold, it showed an advantage in terms of PFS for patients receiving everolims compared with the control group who received octreotide. This initial promising finding was confirmed in the subsequent Radiant-4 trial [25], which clearly demonstrated a benefit in PFS for patients treated with everolimus vs. those receiving placebo. The median PFS was 11 months, and the risk for tumor progression was reduced by 52%. Both studies reported a proportion of objective response rates ranging <10%. Most frequent side effects of everolimus include hyperglycemia, cytopenias, oral ulcers, rash, diarrhea, and atypical infections. Basing on the findings from the above-mentioned trials, everolimus was approved in advanced, progressive, well-differentiated lung and gastrointestinal NETs, thus including intestinal primaries.

15.2.4 Chemotherapy

Cytotoxic agents are the cornerstone of therapy for patients with poorly differentiated NEC, irrespective of the primary tumor site. Given the extreme rarity of NEC rising from the small intestine, their use in this setting of patients is a rare event. As far as well-differentiated intestinal NETs are concerned, disappointing data have been reported by using different chemotherapeutic agents. Well-designed studies in this peculiar clinical scenario are particularly scant, in fact most of the available literature is based on retrospective studies including heterogeneous small series of NET patients.

Even a phase 3 study including 64 patients randomized to receive streptozotocin/5-fluoruracil or interferon failed to demonstrate any difference in terms of PFS and OS between the two groups, and only one patient achieved partial response in the chemotherapy group [26]. Similarly, negligible activity with single-agent or temozolomide-based regimens has been reported by other studies, again confirming that chemotherapy plays a minor role in treatment of intestinal well-differentiate intestinal NETs [27, 28]. To date, there is no evidence of clinical outcome benefit by using systemic chemotherapy in well-differentiated intestinal NETs.

Conversely, chemotherapy might be considered in the setting of highly proliferating tumors, however without good quality scientific data supporting it.

15.3 Liver-Directed Treatments for Hepatic Disease

Several liver-directed approaches have been proposed for treating NETs hepatic metastases, including radiofrequency ablation (RA), trans-arterial embolization (TAE) and trans-arterial chemo-embolization (TACE). The main goal of these treatment is to control symptoms in patients with functioning tumors and related carcinoid syndrome. Potential benefits on patients' survival have been proposed, however with no solid evidence-based data supporting it.

Radiofrequency ablation is a thermal ablative technique based on the cytotoxic effects of high temperature locally administrated in the liver through electrode needles, inducing coagulation necrosis, which can be performed percutaneously under ultrasonography guidance or intraoperatively [29]. This technique has showed to improve symptoms in approximatively 90% of syndromic NET patients, with a relief duration ranging from 14 to 27 months [30]. The treatment-related mortality is below 1%, usually related to uncontrolled carcinoid syndrome exacerbated by ablation, whereas morbidity is around 10%, consisting of hemorrhage, abscess, perforation, bile leakage, and transient live insufficiency [25]. An early computed-tomography is usually performed within the first week after ablation, to identify incomplete ablation and to establish subsequent follow-up. The risk of local disease recurrence is quite high, recurrence rate being reported to range between 5% and 25% [30]. Unfortunately, there is not sufficient amount of prospective trials nor comparative studies able to give reliable information concerning the impact of RA on long-term patient survival.

Other ablative techniques are mainly represented by microwave ablation, cryotherapy, and percutaneous ethanol injection, which however are less frequently performed compared with RA for safety reasons, and due to their lower efficacy.

Trans-arterial embolization (TAE) and chemo-embolization (TACE) consist of the intravascular delivery of therapeutic agents via selective catheter placement under radiological guidance. The rational basis consists of the highly arterial vascularization of NET liver metastases. Trans-arterial embolization (TAE) involves the infusion of embolic agents like lipiodol, absorbable gelfoam particles, or non-absorbable bland microspheres into the artery, which will stop the blood flow. The principle of TACE is to perform intra-arterial injection of cytotoxic agents, usually doxorubicin, or streptozotocin, or a combination of chemotherapy agents before embolization. The treatment consists of multiple embolizations performed every 4–8 weeks, until symptomatic control and/or objective tumor response is achieved. The choice to prefer TAE or TACE in liver metastases from intestinal NETs still remains an unanswered question. Comparing TAE and TACE is difficult because the majority of studies are retrospective, with few patients, including heterogeneous NET populations. A better tolerance has been reported by some authors by using TAE. Concerning efficacy, no significant difference was observed in terms of both objective response and patient's progression-free survival [29–31]. Symptomatic relief is achieved in 60–85% of syndromic NET patients after embolization is performed, whereas objective response is observed in approximatively 50% of patients, with a median PFS of 18–24 months [32]. The most common complication is the so-called post-embolization syndrome, consisting of fever, leukocytosis, abdominal pain, nausea, and transient impairment of liver function tests. Morbidity may be reduced by fractioning treatment in different procedures targeted to embolize each liver segment separately.

Selective internal radiation therapy (SIRT), also known as radioembolization, is a recently developed technique in which 90Y-labeled microspheres are deposited in the hepatic artery. Objective tumor response is reported between 40% and 65% [32]. Again, there is limited data regarding the real impact of this procedure on patients' survival.

15.4 Appendiceal Neuroendocrine Tumors

The appendix is one of the most common sites for NENs. Appendiceal NENs are found in approximatively 0.3%–0.9% of patients undergone appendectomy for acute appendicitis. In a large retrospective analysis performed on 1237 appendectomies, a total of five appendiceal NENs were found, accounting for 0.4% [33]. There is not a specific clinical syndrome related to appendiceal NENs, since the vast majority of them are incidental findings in post-appendectomy specimens. They are slightly more frequent in females, occurring at an average age of 40–50 years; however, they have also been reported in a series of pediatric patients. The prognosis of this kind of NEN is usually excellent, with several series reporting 5-year survival rate of 100% [34]. However, in some cases, they present a more aggressive behavior determining a less favorable patient's clinical outcome. Metastatic disease is a rare event; however, it may occur in those patients with large tumor.

The most powerful prognostic factor of these NENs is tumor size. A diameter above 2 cm is well-recognized as a major negative feature, being associated with presence of metastases in up to 40% of cases [35]. Conversely, tumors sized <1 cm are usually considered with negligible risk of metastases, although some studies have reported few patients with lymph node involvement even in case of such small primary tumors.

International guidelines propose to assess risk profile of appendiceal NENs based on the following criteria: tumor size, specific localization within the appendix, extent of invasion (if any) into the meso-appendix and vascular invasion, proliferative index Ki67 determining tumor grading, lymphatic invasion. Assessing the potential risk of malignancy of appendiceal NENs is pivotal when approaching patients with incidental NEN diagnosed after appendectomy, to understand whether this minimally invasive surgical treatment may be considered curative or not. In the presence of risk factors, right emicolectomy with standard lymphoadenectomy should be performed to prevent the risk of late metastatic occurrence (Fig. 15.2).

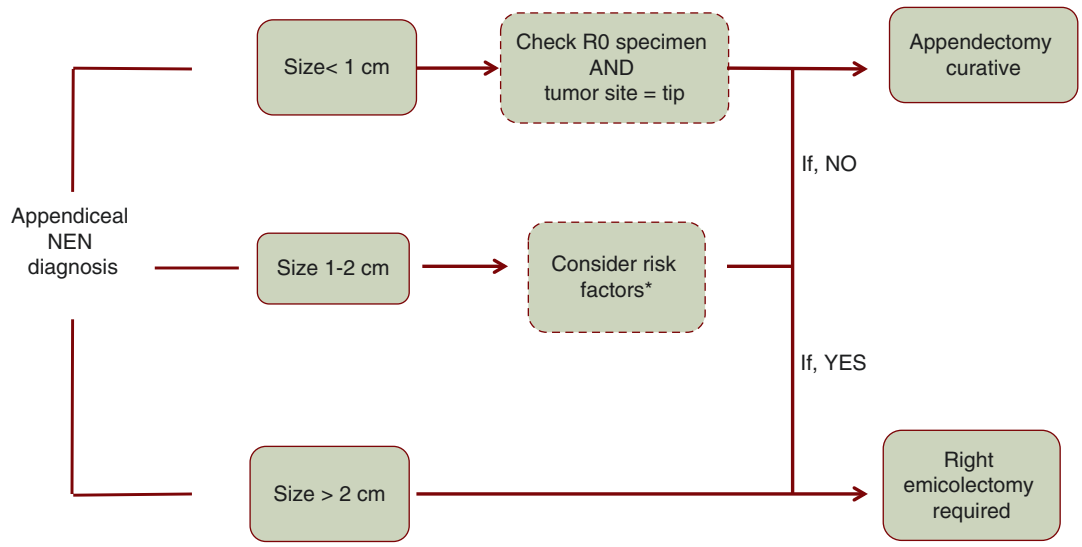

Fig. 15.2 Prognostic stratification and proposed therapeutic approach to appendiceal NENs. Risk Factor: infiltration of mesoappendix (cut-off 3 mm); grading (other than G1); lympho-invasion; angio-invasion

To date, right-emicolectomy with lymph node resection is recommended in those patients with tumor sized >2 cm, if tumors are located at the base of appendix, when the surgical margin is involved after appendectomy (R1 tumors), in selected cases with tumor sized <2 cm if risk factors are present (>3 mm infiltration of meso-appendix, presence of lympho-angioinvasion, grading G2) (Fig. 15.2) [34]. However, planning the optimal treatment for appendiceal NENs with small tumors and presence of risk factors remains a clinical challenge. In a recent multicenter large retrospective analysis, tumor size >1.5 cm, grading G2 (Ki67 3–20%) and lympho-vascular infiltration were independent risk factors related to nodal metastases, suggesting that in the presence of at least one of these factors, right emicolectomy should be suggested [35].

Although the majority of tumors <2 cm do not harbor any risk to develop metastases and may be considered cured after appendectomy, several controversies remain for some of these patients, in whom several risk factors have been identified. Those patients may have to undergo an additional operation and a proportion of them will need long-term follow-up [36]. Well-designed clinical trials, with long-term patients' follow-up, are definitively understand the prognostic impact of those risk factors which could be associated with regional or distant metastases and potentially adverse outcomes [36].

15.5 Conclusions

Clinical management of intestinal NETs still remains a challenge for physicians dealing with this rare kind of cancer. In the last decades, therapeutic landscape of these tumors has dramatically changed, given the introduction novel therapies (Fig. 15.1), including targeted agents and radiolabeled compounds, which may be used when the first-line therapy based on somatostating analogs fails to control tumor growth. Peptide receptor radionuclide therapy is an established treatment for progressive intestinal G1 and G2 NETs, with solid scientific data confirming its ability to induce tumor regression and prolong both progression-free survival and overall survival. Ablative liver-directed treatments may be helpful to reduce hepatic tumor load and to control symptoms in functioning tumors.

Appendiceal NETs need to be separately considered, given their peculiar biology and frequent indolent behavior. In these tumors, an accurate prognostic stratification is mandatory to reduce the risk of tumor recurrence and to avoid unnecessary surgical procedures.

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