Appendiceal neuroendocrine neoplasms: diagnosis and management

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Abstract

Gastrointestinal neuroendocrine neoplasms (GI-NENs) are increasingly being recognised, while appendiceal NENs (aNENs) currently constitute the third most common GI-NEN. Appendiceal NENs are generally considered to follow an indolent course with the majority being localised at diagnosis. Thus, the initial surgical approach is not that of a planned oncological resection. Due to the localised nature of the disease in the majority of cases, subsequent biochemical and radiological assessment are not routinely recommended. Histopathological criteria (size, mesoappendiceal invasion, Ki-67 proliferation index, neuro- and angio-invasion) are mainly used to identify those patients who are also candidates for a right hemicolectomy. Goblet cell carcinoids are a distinct entity and should be treated as adenocarcinomas. Despite the absence of any substantial prospective data regarding optimal management and follow-up, recent consensus statements and guidelines have been published. The purpose of this review is to overview the published studies on the diagnosis and management of appendiceal NENs and to suggest a possible management protocol.

Key Words
- neuroendocrine
- neoplasm
- appendiceal
- appendicectomy
- right hemicolectomy
- carcinoid

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Introduction

Neuroendocrine neoplasms (NENs), previously named 'carcinoid' tumours, most frequently occur in the gastrointestinal (GI) tract (54.5%) and have been an area of ongoing interest in the field of many different disciplines including endocrinology, surgery, oncology, radiology and nuclear medicine (Maggard *et al.* 2004). These tumours are thought to arise from neuroendocrine (NE) cells (Kulke & Mayer 1999), predominantly enterochromaffin or Kulschitsky cells, which exhibit different histopathological features and hormone-secreting capacity according to the primary site of origin (Creutzfeldt 1996, Alexandraki & Kaltsas 2012).

Gastrointestinal neuroendocrine neoplasms (GI-NENs) are increasingly being recognised, with an estimated incidence in the range of 2–5 cases/100 000/year (Yao *et al.* 2008, Niederle *et al.* 2010, Fraenkel *et al.* 2012). While previous epidemiological data considered appendiceal NENs (aNENs) to be the most common GI-NENs, the overall percentage has decreased from 17–28% to 2–5% of total NENs, following the overall increase in the relative incidence of other NENs, such as gastric and rectal, reflecting the increasing number of endoscopic procedures performed. However, in absolute terms the incidence of aNENs has increased over the past decade by 70–133%

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(Hauso *et al*. 2008, Yao *et al*. 2008) attaining in 2011 an incidence as high as 6.7 of 100 000 persons (Shaib *et al*. 2015) possibly due to the increased number of laparoscopies performed, in particular during gynaecological surgery (Giesteira *et al*. 1980, Heller *et al*. 1999, Hauso *et al*. 2008). Observational studies have shown that the natural history of these neoplasms is rather indolent, with only a minority developing extensive disease (Mullen & Savarese 2011). For this reason, there has been considerable debate as to whether these patients should be investigated for the presence of residual disease and the intensity and duration of subsequent follow-up (Plockinger *et al*. 2008, Pape *et al*. 2012, Grozinsky-Glasberg *et al*. 2013). Goblet cell carcinomas (GCCs) are no longer regarded as a subset of aNENs but exhibit characteristics of both NENs and appendiceal adenocarcinomas, differing substantially in respect of their natural history, treatment and prognosis. They should be treated as adenocarcinomas and will not be discussed further in the present review (Pape *et al*. 2012).

Epidemiology

The majority of epidemiological studies has recently shown that the appendix is the third more frequent site of GI-NENs (16.7%), after the small intestine (44.7%) and the rectum (19.6%) (Crocetti 1997, McCusker *et al*. 2002, Maggard *et al*. 2004, Landry *et al*. 2008). However, aNENs may be under-reported in several series or may not even be registered in any cancer database as they are considered to be indolent (Van Eeden *et al*. 2002, Hauso *et al*. 2008, Alexandraki & Kaltsas 2012). Indeed, in the Surveillance, Epidemiology and End Results (SEER) series, only neoplasms considered as malignant are included, with aNENs displaying a very low prevalence (McCusker *et al*. 2002). However, in the paediatric series where NENs are extremely uncommon, aNENs represented the second most common type of GI-NEN (Parkes *et al*. 1993, Corpron *et al*. 1995, Bethel *et al*. 1997, Scott & Upadhyay 2011).

In both adults and children, aNENs are usually diagnosed incidentally, during or after surgical treatment for acute appendicitis or other abdominal conditions (Moertel *et al*. 1990, Parkes *et al*. 1993, Corpron *et al*. 1995, Bethel *et al*. 1997, Plockinger *et al*. 2008, Scott & Upadhyay 2011, Pape *et al*. 2012). The rate of aNENs presence in patients undergoing appendicectomy is reported to be 0.3–0.9% (Moertel *et al*. 1968, Connor *et al*. 1998, Tchana-Sato *et al*. 2006, Debnath *et al*. 2008, In't Hof *et al*. 2008, Shapiro *et al*. 2010, Yilmaz *et al*. 2013); however, in some series, it has been reported to be as high as 2.3% (Hatzipantelis *et al*. 2010, Ozer *et al*. 2011, Van Gompel *et al*. 2007) or as low as 0.16% (Coskun *et al*. 2006, Doede *et al*. 2000). The prevalence of aNENs among primary malignant lesions of the appendix ranges between 43 and 57% (Schmutzer *et al*. 1975, Connor *et al*. 1998). Interestingly, in the SEER database, the prevalence of aNENs among all appendiceal neoplasms ranged between 17.3 and 19.7% until 1998–2001 (McCusker *et al*. 2002, McGory *et al*. 2005), then were substantially reduced to 9.4% because only 'malignant' neoplasms were included (Hsu *et al*. 2013). This latter SEER analysis included 2812 patients harbouring appendiceal tumours with NE differentiation; the most common histologic subtype was GCCs (59.6%), followed by malignant aNENs (32.1%) and composite GCC-adenocarcinoma (6.9%) (Hsu *et al*. 2013). Furthermore, among 6824 black patients who underwent an appendicectomy, a similar prevalence (47.6%) of aNENs and benign non-endocrine cell tumours was reported (45.2%) (Coskun *et al*. 2006). In a recent study from SEER, a higher proportion of white patients was observed in aNENs, but the difference was not statistically significant (Shaib *et al*. 2015).

In terms of patient characteristics, a slightly higher incidence among females (Shaib *et al*. 2015) has been shown in most but not all epidemiological studies (Sandor & Modlin 1998, Hemminki & Li 2001, Prommegger *et al*. 2002, Van Gompel *et al*. 2007, Landry *et al*. 2008, Turaga *et al*. 2012) – a fact that has been attributed to the increased rate of surgical interventions performed in women (Moertel *et al*. 1968, Shapiro *et al*. 2010, Carpenter *et al*. 2012). A possible hormonal influence has not been proven (Graham *et al*. 2009). An epidemiological study from Sweden covering the years 1958–1998 showed that, of 5184 NENs, the appendix was the main site of involvement in women, whereas the SI was the main site in men; aNENs showed an unusually early onset with a maximum incidence at age 15–19 years in women and 20–29 years in men (Hemminki & Li 2001). Indeed, aNENs are diagnosed at a much younger age of 32–42.2 years (Hemminki & Li 2001, McGory *et al*. 2005, Graham *et al*. 2009, Benedix *et al*. 2010, Turaga *et al*. 2012, Hsu *et al*. 2013) compared to other GI-NENs and all other appendiceal neoplasms, which are diagnosed at an average age of 62.9 and 61.9 years, respectively (Sandor & Modlin 1998). In a large series from The Netherlands, the appendix was the most frequently diagnosed primary site of NENs in patients <35 years (Quaedvlieg *et al*. 2001). Similar findings were reported in an old, small series from Sweden (Ahlberg *et al*. 1980). Moertel *et al*. (1987) reported that patients with larger tumours and metastatic disease were

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younger than those with smaller and clinically benign tumours; the median age of patients with tumours ≥2.0 cm was 31 years, and those with metastases was 29 years, as compared with a median age of 42 years in patients with non-metastatic tumours <2.0 cm.

Pathogenesis

Appendiceal NENs arise from subepithelial NE cells that are present in the lamina propria and submucosa of the appendix wall (Lundqvist & Wilander 1986, Shaw 1991) (Figs 1 and 2). Masson first identified the subepithelial cells as the origin of aNENs and demonstrated that these neurosecretory cells exhibit both endocrine and neural characteristics as integral parts of the subepithelial nervous plexus (Masson 1928, Sandor & Modlin 1998). These cells are more numerous at the tip of the appendix, as opposed to epithelial NE cells, which are equally distributed at all sites within the appendix; the density of these NE cells is low in infancy and increases with age (Shaw 1991). The distinctive features of these tumours compared to NENs originating from other sites may be attributed to their different origin and may relate to their more favourable prognosis and indolent course (Shaw 1990, 1991, Stinner & Rothmund 2005). Their subepithelial origin may also explain their smaller size and younger age at presentation, along with unique histopathological features such as S-100 expression (Goddard & Lonsdale 1992, Moyana & Satkunam 1992).

Molecular pathology

Several gene transcripts have been measured by quantitative RT-PCR (qRT-PCR) in malignant aNENs. Elevated chromogranin A (CgA) transcript and protein levels were found in samples of tissue showing acute appendicitis but without any histological evidence of a tumour, implying that CgA expression may identify covert lesions

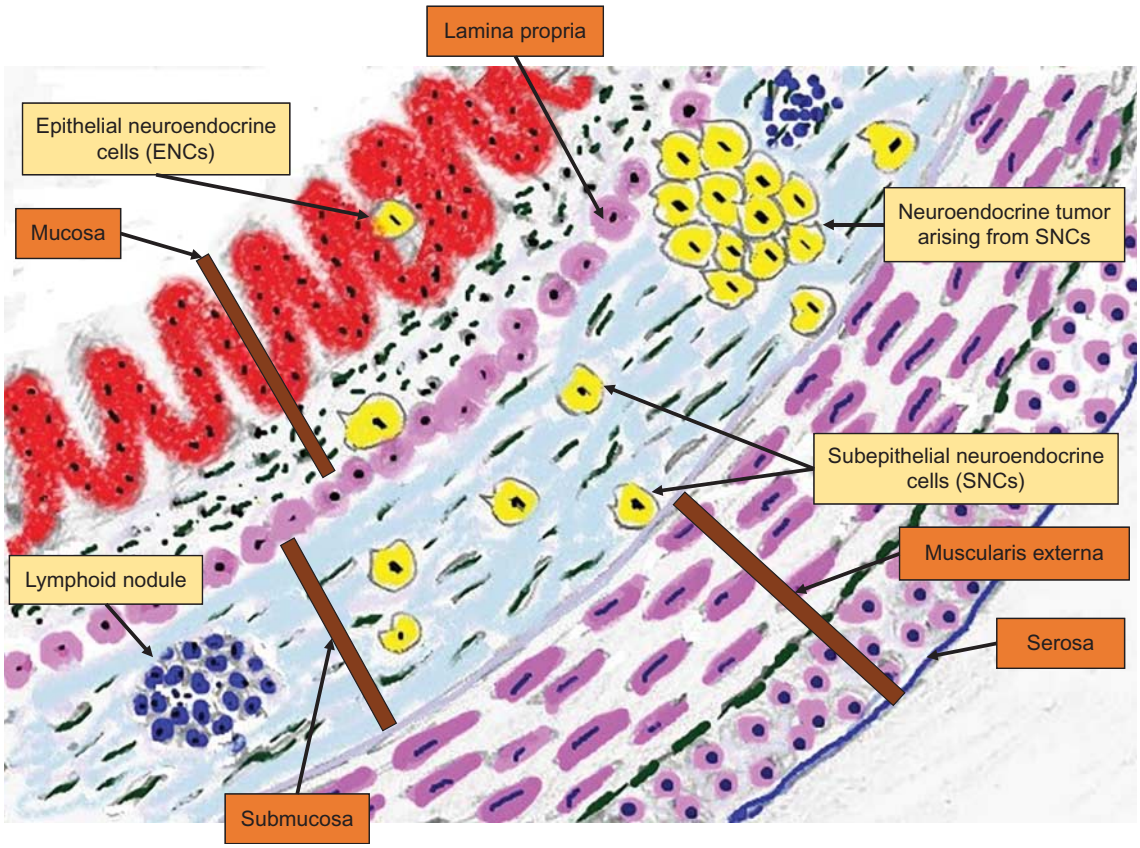

Figure 1
A cross-section of the appendix showing the four layers that form the appendiceal wall: serosa, muscularis externa, submucosa and mucosa. Neuroendocrine cells are located in the mucosa (Epithelial neuroendocrine cells (ENCs)) and in the submucosa (subepithelial neuroendocrine cells (SNCs)).

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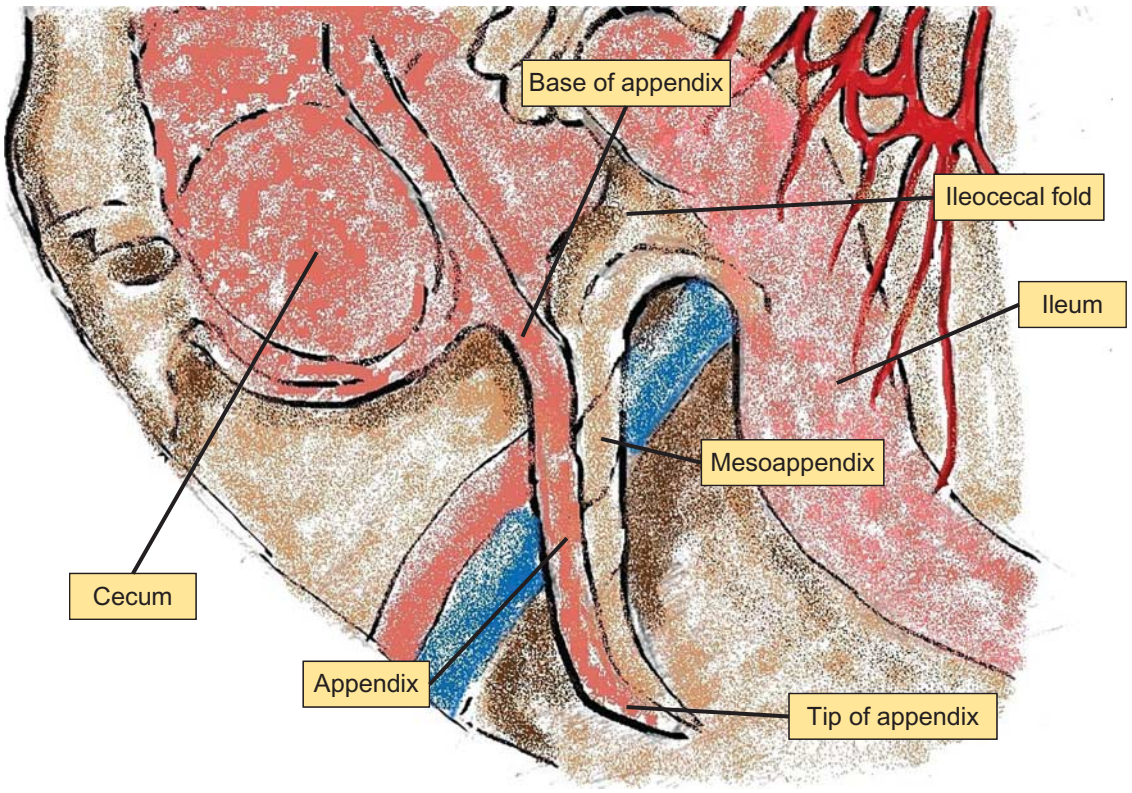

Figure 2
Anatomy of the appendix and surrounding organs.

(Modlin *et al*. 2006). Other molecular markers have also been also studied (Modlin *et al*. 2006) (Supplementary Table 1, see section on supplementary data given at the end of this article).

Clinical presentation

The clinical presentation of aNENs was indistinguishable from acute appendicitis in over 54% of patients (Roggo *et al*. 1993, Prommegger *et al*. 2002), while histopathology revealed the presence of obstructive features in only 25% of cases (O'Donnell *et al*. 2007). However, as the majority of aNENs are located at the tip of the appendix, it is not surprising that they rarely cause obstruction, as opposed to the minority located at the base, which can lead to luminal obstruction (Moertel 1987, Moertel *et al*. 1987, Goede *et al*. 2003). Indeed, less common presentations of aNENs include non-specific abdominal pain in the right lower abdomen due to intermittent partial luminal obstruction caused by the tumour (Prommegger *et al*. 2002, Goede *et al*. 2003, Modlin *et al*. 2003, O'Donnell *et al*. 2007). The carcinoid syndrome (CS) is exquisitely rare in patients with aNENs (Liu *et al*. 2010, Grozinsky-Glasberg *et al*. 2013), which is mostly encountered along with metastases as in the case of other GI-NENs; other functional syndromes have been described in only a few case reports (Supplementary Table 2, see section on supplementary data given at the end of this article).

Diagnosis: risk stratification

Imaging features

Primary aNENs elude radiological detection until they are large enough to be evident on computerised tomography (CT) scanning (Wallace *et al*. 1996). Double-contrast GI studies, either CT or magnetic resonance imaging (MRI), exhibit the highest sensitivity in identifying primary neoplasms (Sundin *et al*. 2009, Pape *et al*. 2012). Imaging of the abdomen and pelvis has been the standard means to assess local and distant spread and, along with somatostatin receptor imaging (SRI), are used as staging imaging modalities for GI-NENs (Kwekkeboom *et al*. 2009, Sundin *et al*. 2009, Pape *et al*. 2012). However, in a small

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retrospective study, preoperative CT could not localise aNENs in any of ten patients studied (Coursey *et al*. 2010). Moreover, SRI with ^{111}In-pentetreotide (Octreoscan) has not been found to be useful in identifying small NENs (Kisker *et al*. 1996, Kloppel *et al*. 2009, Kwekkeboom *et al*. 2009), but it has been successful for visualising extra-hepatic and extra-abdominal tumour spread; SRI has been suggested in all patients with a known NEN except for aNENs measuring <1 cm in diameter (Kisker *et al*. 1996). It should be considered that a false positive Octreoscan may result by respiratory infections, concomitant granulomatous disease, adrenal uptake, an accessory spleen and surgical scars (Kwekkeboom *et al*. 2009); it is advisable to perform a scan >3 months post-operatively to reduce the false positive rates from previous surgical inflammation. Overall, SRI may be considered in aNENs with risk factors for a more aggressive disease. Whether radiolabelled octreotide with ^{68}Ga-DOTATOC provides a better spatial resolution and a higher ratio of tumour-to-normal tissue than the SRI and single-photon emission CT (SPECT) for detecting aNENs remains to be proved (Gabriel *et al*. 2007, 2009, Sundin *et al*. 2009).

Biochemical markers

CgA is currently the most useful general biomarker available for the diagnosis of GI-NENs because elevations in CgA have been found to predict a relapse that may precede radiological detection as it is co-secreted by the majority of NE tumoural cells and persists after malignant transformation (Kaltsas *et al*. 2004). As there is a close correlation of the level of CgA elevation and tumoural load, and because the size of aNENs in the great majority is <2 cm (Moertel *et al*. 1987, Roggo *et al*. 1993), CgA levels are generally within the normal range in patients with aNENs (Alexandraki *et al*. 2011, Grozinsky-Glasberg *et al*. 2013) and its value as a screening tool has not been proven (de Herder 2007, Alexandraki *et al*. 2011). In the past, neuronal specific enolase (NSE) has also been suggested as a marker for aNENs, but its utility has not been confirmed (Moertel 1987). Routine screening for 5-hydroxyindoloacetic acid (5-HIAA) excretion has not been recommended except where the rare presence of CS is suspected (Grozinsky-Glasberg *et al*. 2013).

Classic and novel histopathological neuroendocrine markers

In 83% of aNENs, CgA immunoreactivity was detected in >50% of tumour cells (Perez *et al*. 1990), while NSE and CD56 are also expressed (Jiang *et al*. 2011). Novel pathological markers have been recently used in an attempt to identify the tissue of origin of metastatic foci and/or the malignant potential of certain GI-NENs (Katsetos *et al*. 1994) (Supplementary Table 3, see section on supplementary data given at the end of this article).

Appendiceal NENs share some common characteristics with GCCs, but have a much stronger CgA expression and a lower Ki-67 (Alsaad *et al*. 2007, Jiang *et al*. 2011). Other immunohistochemical markers of aNENs include 25–50% expression for CK20 in 16% of the tumour cells compared to GCCs, which exhibit strong and diffuse immunopositivity for CK20, while a 5–50% expression of CK7 in 70.5% of tumour cells was seen only in GCCs (Alsaad *et al*. 2007). The coexistence of both entities in the same appendix suggested a closer histogenetic relationship or two independent primaries (collision tumours)(Chetty *et al*. 2010).

Less common aNEN subtypes include those composed of clear cells along with an abundant lipid accumulation (La Rosa *et al*. 2010) that need to be distinguished from GCCs or signet ring adenocarcinomas (Chetty & Serra 2010). Another rare variant is the tubular aNEN, which needs to be carefully characterised because small infiltrating tubules may raise the possibility of metastatic adenocarcinoma (Matsukuma & Montgomery 2012).

Histopathological features used to identify high-risk neoplasms

Histopathological documentation is the identifying feature of aNENs. Following the identification of an aNEN, a number of histopathological parameters have been used to differentiate tumours destined to follow an indolent course from those at risk of relapse or the development of metastatic disease.

Size Tumour size has been traditionally considered the most reliable indicator of the malignant potential of aNENs (Anderson & Wilson 1985, Goede *et al*. 2003). An analysis of a large series of aNENs demonstrated that a tumour size >2 cm (greatest dimension) represents one of the most valuable predictive factors of lymph node (LN) metastasis (Groth *et al*. 2011, Pape *et al*. 2012). The great majority of aNENs (95%) are <2 cm in diameter: 60–85% are <1 cm and 4–27% are 1–2 cm, whereas only 2–17% are >2 cm (Moertel *et al*. 1987, Roggo *et al*. 1993). The risk of metastases in tumours <1 cm in diameter has been traditionally considered to be virtually zero (Stinner *et al*. 1996, Murray *et al*. 2014). In one small retrospective study

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of patients with tumours <1 cm in which a simple appendicectomy was performed, no patient was found to have evidence of residual disease or recurrence after a median follow-up period of 5 years (range: 6 months–15 years) (Murray *et al.* 2014). Several studies report metastatic rates as low as 0–1% in tumours measuring 1–2 cm as opposed to tumours >2 cm, which may develop mostly regional metastases in 20–85% (Stinner *et al.* 1996, Stinner & Rothmund 2005, Mullen & Savarese 2011). Concerning tumour size, early studies reported that no patient with a tumour <2 cm treated with a simple appendicectomy developed recurrent or metastatic disease after a median follow-up period >26 years, while a moderate degree of local invasion was not associated with an adverse overall prognosis (Moertel *et al.* 1987). An old series originating from the Mayo Clinic revealed that 21% of 150 aNENs with tumours 2–3 cm and 44% of those measuring >3 cm in diameter had metastasised, whereas no metastases were observed in tumours measuring <2 cm (Moertel *et al.* 1987). While one may question the methodology in assessing the presence of residual disease in the older studies, the lack of modern imaging criteria is balanced by the advantage of the extensive clinical follow-up, thus suggesting that such small tumours very rarely lead to clinically significant adverse outcomes (Moertel *et al.* 1987). However, in another early series that included 147 aNENs, only two patients with lesions >1.5 cm but <2 cm in size had evidence of metastatic spread at the time of presentation (Anderson & Wilson 1985). Early case reports and small case series have described metastases in lesions <1 cm (Pearlman & Srinivasan 1971, Andersson & Bergdahl 1977, MacGillivray *et al.* 1992). More recent series report rather different findings; in one case series, including eight patients who had a completion right hemicolectomy (RHC) in aNENs <1 cm in diameter, LN involvement was found in a single patient (12.5%); larger tumours ≥2 cm had a 57.1% (4 out of 7) rate of LN metastasis, while tumours with a size in the 'grey zone' (indeterminate risk) had an intermediate metastatic rate of 38.5% (5 of 13) (Grozinsky-Glasberg *et al.* 2013). In addition, a more recent analysis of the SEER database reported a much higher than expected rate of LN metastases in 4 of 27 patients (15%) with tumours ≤1 cm, 16 of 34 patients (47%) with tumours >1 cm but ≤2 cm and 24 of 28 patients (86%) with tumours >2 cm (Mullen & Savarese 2011). Size remains a highly significant factor in predicting the risk of aNENs developing metastatic disease (Groth *et al.* 2011, Pape *et al.* 2012), but extrapolation to the need for a more aggressive surgical intervention in larger tumours is still questionable (Grozinsky-Glasberg *et al.* 2013) (see below).

Location The localisation of aNENs also seems to exert a significant prognostic role. Approximately 60–80% of aNENs are localised at the tip of the appendix, 5–21% in the body and 7–10% at the base (Roggo *et al.* 1993, Prommegger *et al.* 2002, Safioleas *et al.* 2005, Fornaro *et al.* 2007). Because an incomplete resection is most likely to occur at the base of the appendix, such lesions are more likely to develop local recurrence compared to those located at the tip following a simple appendicectomy (Sutton *et al.* 2003, Alexandraki *et al.* 2011). In a small series of 12 patients who underwent a RHC, 5 (42%) had their neoplasm in the appendiceal base and 2 (40%) of these had residual disease (Alexandraki *et al.* 2011). Similarly, a subsequent multicentric study, addressing the same issue but including a larger number of patients, confirmed these findings: of the 33% of the tumours located at the base of the appendix, metastases were identified in 44% (Grozinsky-Glasberg *et al.* 2013).

Mesoappendiceal invasion Mesoappendiceal invasion (MAI) represents an extension of the tumour invading the serosa to the pericolic (mesoappendiceal) fat; the mesoappendix is a fold of peritoneum around the appendix (Fig. 2). Despite the fact that serosal involvement is not considered an aggressive feature of aNENs, MAI has been considered as a poor prognostic factor and a relative indication for RHC, but in several studies no recurrence after simple appendicectomy was reported (Syracuse *et al.* 1979, Dall'Igna *et al.* 2005). Syracuse *et al.* (1979) emphasised the value of close examination of the mesoappendix for evidence of invasion, because 13 (14%) of 92 patients had MAI and 15% (two of 13) of them developed nodal metastases that were identified after ileocolectomy (Syracuse *et al.* 1979); one neoplasm was 1 cm and the other 1.5 cm, whereas, in the same series, in one neoplasm 4 cm in size, no LN invasion by the NEN was recognised after the ileo-colectomy. In an older series, four of 41 patients had evidence of tumour extension and MAI, but only one with a tumour >2 cm had local LN metastases and was submitted to RHC (Roggo *et al.* 1993). In another recent small series of 12 patients who underwent RHC, 50% had MAI, and in 17% of those (one of six), one positive LN was identified (Alexandraki *et al.* 2011). Extending these latter data to a multicentric study, 75% of patients had MAI independent of the depth, as there are no clear data in the literature to substantiate that 3 mm is the valid size limit for performing or not

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performing an extended operation, and in 38% (eight of 21), LN metastases were found (Grozinsky-Glasberg *et al.* 2013). Indeed, in this latter study, five of 13 patients with a tumour size between 1 and 2 cm (38%) presenting with MAI <3 mm had metastatic disease to LNs at RHC. Thus, no clear correlation was documented between tumour size and the depth of MAI, questioning the arbitrary definition of 3 mm as suggested by European Neuroendocrine Tumor Society (ENETS) guidelines (Pape *et al.* 2012). In contrast, other studies did not find that MAI predicts residual or metastatic disease. Hence, in a paediatric series, 30% of 23 patients had MAI, and despite the fact that only two children underwent a RHC and one more underwent the removal of a residual appendiceal stump, no extra-appendiceal disease was found in the RHC specimens; in addition, no recurrences or metastatic disease were identified after a median follow-up period of 26 years (range: 9 months to 51 years) (Moertel *et al.* 1990).

Additional factors Tumour proliferation markers may predict metastatic potential (Solcia *et al.* 1999, Liu *et al.* 2010, Alexandraki *et al.* 2011, Pape *et al.* 2012), and a high Ki-67 proliferation index (Ki-67) has been shown to be predictive of aggressive biological behaviour in GI-NENs (Van Eeden *et al.* 2002). Hence, it has been suggested that a raised mitotic index and/or a high Ki-67 may be indicative of a more malignant behaviour in aNENs and could thus also be considered as an indication for RHC (Moertel 1987, Pape *et al.* 2012). Increased Ki-67 was associated with decreased survival (Liu *et al.* 2010); no correlation was demonstrated between Ki-67 and tumour size or presentation with metastatic disease. Moreover, a recent multicentre study that included patients who had undergone an RHC reported that 17% had a Ki-67 >2% and 50% of them (2 of 4) had LN metastases (Grozinsky-Glasberg *et al.* 2013). Vascular invasion, another additional factor for aNEN aggressiveness, was found in 10 (3.6%) patients and 6 (60%) harboured LN metastases. Finally, 6 patients had perineural invasion and 2 (33%) of them harboured LN metastases (Grozinsky-Glasberg *et al.* 2013).

Metastatic disease

Historically, the presence of regional LN metastases from an aNEN has mainly been reported in isolated case reports, including 14-year-old children (Supplementary Table 4, see section on supplementary data given at the end of this article) (Kieraldo *et al.* 1963, Skaane & Eide 1977, Deeg *et al.* 2003, Cernaianu *et al.* 2010). When the primary tumour involves the appendix wall diffusely, lymphatic permeation to the regional LN was reported in 50% of 21 cases (Dunn 1982). Similarly, small series revealed regional LN metastases in 8.8% of 46 patients (Glasser & Bhagavan 1980), 3.3% of 30 patients (Wackym & Gray 1984), 2.4% of 41 patients (Roggo *et al.* 1993), 4% of 25 paediatric and finally metastatic spread was reported in 1.4% of 147 patients (Anderson & Wilson 1985) or 8% from 12 aNENs (Fucs *et al.* 2005). Moreover, LN metastases from primary aNENs <2 cm in diameter have been reported (Thirlby *et al.* 1984), while MAI was reported as the only aggravating factor to suggest potentially aggressive behaviour in one case report with liver metastasis occurring after appendicectomy from a 0.6 cm aNEN (MacGillivray *et al.* 1992).

More recently, the majority of information regarding metastatic disease of aNENs has been obtained from the SEER database with extracted data including demographic characteristics (age, sex and race), histologic tumour type, tumour size, degree of extension, LN involvement and tumour stage using the SEER staging system (localised, regional and distant), the most invasive surgical treatment rendered in the first 4 months after diagnosis and overall survival (OS) (Moertel *et al.* 1987). Mullen *et al.* found an unexpectedly high incidence of regional LN metastases in patients with typical aNENs ≤2.0 cm, rating regional LN metastases at 49% (44 of 89) of patients (Mullen & Savarese 2011). As opposed to this very high rate, in an older series from the same database, LN metastasis was found in 24% of the patients, and distant metastatic disease in 10% of 900 patients with aNENs (Landry *et al.* 2008). In another analysis of 1570 patients from three different databases, different rates of non-localised disease have been reported: 35.4% (26.8% regionalised, 8.5% distant metastatic disease) was reported in the SEER (1973–1991) registry compared to 5% (3.8% regionalised, 0.7% distant metastatic disease) in the End Result Group (ERG:1950–1969) (Sandor & Modlin 1998). The differences in the above numbers may be due to the completeness of the pathological data taken into consideration in several series, the definition of aNEN, the fact that pathologists usually do not report as malignant the incidentally discovered small aNENs without obvious nodal involvement or finally the improved tumour detection, especially in regard to covert metastases; it should be noted that complete pathologic data were not routinely included in the SEER database prior to 1988 (Modlin & Sandor 1997, Mullen & Savarese 2011). As opposed to these high rates taken from the

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SEER database, 1.6% of 619 patients with aNENs from a Netherlands series had distant metastases at the time of diagnosis (Quaedvlieg *et al.* 2001).

In a paediatric series, 2.4% of 41 patients had LN metastases combining both a size >2 cm along with an origin from the base of the appendix (Roggo *et al.* 1993). Age, gender and depth of tumour invasion did not predict LN involvement, whereas tumour size was a significant predictor of nodal involvement: LN metastases were present in 15% of patients with tumours ≤1.0 cm in diameter, 47% with tumours >1 cm but ≤2 cm in diameter and 86% with tumours >2 cm in diameter (Mullen & Savarese 2011).

Treatment

The management of aNENs depends on the size and degree of extension of the primary lesion. Considering that these tumours are usually very small lesions, their diagnosis usually coincides with their resection, and no further action is required. Laparoscopic approaches are increasingly used for appendicectomy and RHC. The laparoscopic appendicectomy for appendiceal tumours seems to have a slightly higher rate of inadequate resection, but it is not associated with significantly worse patient prognosis than open appendicectomy (Bucher *et al.* 2004).

As previously mentioned, the great majority of patients have localised disease. Despite the fact that the tumour node metastasis staging system has been adopted from ENETS, it is still not in widespread use in the registration of the pathologic features of aNENs (Supplementary Table 5, see section on supplementary data given at the end of this article). Any patient undergoing appendicectomy should have a full examination of the small bowel at the time of surgery, and histopathological assessment of the resected appendix should include location, size and the detailed nature of any tumour, as well as the presence of MAI or angio- and/or neuro-invasion along with Ki-67 assessment (Pape *et al.* 2012, Sutton *et al.* 2003).

In this specific staging system, stage I tumours require no further action as simple appendicectomy is most frequently curative and sufficient (Pape *et al.* 2012). However, as opposed to previous suggestions and after taking in consideration more recent evidence, for stage IIa tumours ≤2 cm invading submucosa, muscularis propria and/or minimally (up to 3 mm) invading subserosa/mesoappendix tumours when >1 cm but ≤2 cm, we feel that RHC should be considered as an option to the patients when they have an additional risk factor such as MAI or base involvement, because patients are relatively young and long-term longitudinal prospective studies are not available; these patients should be informed about the lack of evidence regarding the stage of their disease and for the recent data that put them in a grey zone (Grozinsky-Glasberg *et al.* 2013). In cases of incomplete resection (R1) or tumour location at the base of the appendix, completion RHC could be an option; the patient should be informed regarding the higher complication rate and the perioperative risks. However, in series with patients followed as long as 30 years, only one had residual microscopic disease in the appendiceal stump after appendicectomy alone (Bowman & Rosenthal 1983). Further criteria in favour of completion surgery such as a Ki-67 ≥3% (NEN G2) or the presence of angio- or neuro-invasion have also been suggested (Liu *et al.* 2010, Pape *et al.* 2012).

For stage IIb, RHC is recommended due to the increased risk of LN metastasis and the chances of long-term tumour recurrence and/or distant metastasis (Mullen & Savarese 2011). There are a few cases in which RHC was the initial surgical intervention when the neoplasm was grossly evident and the diagnosis was made preoperatively (Deeg *et al.* 2003, Gilboa *et al.* 2008, Coursey *et al.* 2010, Murray *et al.* 2014).

Histological identification of residual disease after RHC completion appendicectomy have reported rates 12–36% (10 of 28, 3 of 12, 5 of 28) (Gouzi *et al.* 1993, Alexandraki *et al.* 2011, Grozinsky-Glasberg *et al.* 2013). Thus, contrary to the older series supporting simple appendicectomy as adequate treatment (Shaw 1991), more caution is required, particularly in this young population (Roggo *et al.* 1993, Rothmund & Kisker 1994, Stinner *et al.* 1996). On the other hand, morbidity rates for RHC range between 17 and 37%, particularly respiratory and cardiovascular complications in the elderly (usually not the case for aNENs) or after a reoperation is performed in younger patients because of bowel occlusion (Bokey *et al.* 1995, Alexandraki *et al.* 2011). No guidelines currently exist for the management of specific aNEN cases, such as with a perforated appendix; in a published case, the authors suggested RHC to avoid dissemination (Mathur *et al.* 2012).

Two recent studies were designed to perform a formal RHC to remove the primary tumour with LN resection as a staging procedure when only one of the criteria reported by Sutton was met (Pape *et al.* 2012; Sutton *et al.* 2003): largest diameter >2 cm, location in the base of the appendix, MAI, the presence or angio-/neuro-invasion, or a Ki-67 >2% (Alexandraki *et al.* 2011, Grozinsky-Glasberg *et al.* 2013). However, at present, there is no

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evidence to show that such a procedure improves symptom control or survival or that RHC prevents additional distant metastases from those occurring in patients with distant metastatic disease at presentation (Mullen and Savarese 2011).

Regarding the type of surgery, in a recent study from the SEER database of 510 patients with localised disease, 7.8% had appendicectomy only, 50.2% RHC and 43% other surgery; of 300 patients with regional disease, 2.6% had simple appendicectomy, 70.7% RHC and 26.7% other surgery; all patients with distant disease had debulking surgery (Shaib *et al*. 2015).

For the minority of patients who present with more extensive (stage III and VI) disease, surgery with curative intent should always be considered, when possible (Pape *et al*. 2012). Moreover, there are currently a number of systemic therapies available for patients with disseminated disease (Alexandraki & Kaltsas 2012, Pape *et al*. 2012). Recent findings of patients with advanced aNENs (Grozinsky-Glasberg *et al*. 2013) have shown that treatment with somatostatin analogues (SSAs) is associated with more prolonged progression-free survival compared to placebo (Pape *et al*. 2012). Because aNENs seem to have a better prognosis than other GI-NENs, even in the presence of extensive disease, treatment with these agents seems an appropriate first-line approach (Pape *et al*. 2012). For patients with progressive disease despite treatment with SSAs, further therapeutic modalities may be employed. Loco-regional therapies with embolisation and/or radiofrequency ablation could be utilised in patients with predominant hepatic metastases; the administration of molecular targeted therapies and radiopharmaceuticals could be also employed (Pape *et al*. 2012). Although traditionally GI-NENs other than pancreatic NENs are not considered to be chemosensitive, recent data have suggested that they may also respond to temozolomide-based chemotherapy (Koumarianou *et al*. 2015). Interestingly, a 25-year-old woman with aNEN was treated with intraperitoneal cisplatin for peritoneal recurrence after a fertility-sparing cytoreductive procedure; 5 years after her procedure, she had a successful second pregnancy implying a good long-term outcome (Smaldone *et al*. 2007).

Regarding the small number of functional aNENs reported, treatment with SSAs should be administered (Kaltsas *et al*. 2004, Alexandraki & Kaltsas 2012). However, because of the rarity of these cases, precise indications and the duration of such treatment have not been defined (Pape *et al*. 2012).

Prognosis

Demographic and clinical data have revealed that aNENs have significantly better outcomes compared to other neoplasms of the appendix (McGory *et al*. 2005), while the patients are younger, more often female, with a higher percentage of localised disease, as previously discussed. This relatively benign course may reflect the anatomic site, its early detection and resection, the biology of the tumour itself (Modlin *et al*. 2005) or the tumour stage (localised or metastatic disease: regional or distant) and size resulting in a higher 5-year survival and a better outcome than NENs at other sites (Sandor & Modlin 1998, McCusker *et al*. 2002, O'Donnell *et al*. 2007, Benedix *et al*. 2010) (Supplementary Table 6, see section on supplementary data given at the end of this article). There are very few reports describing a fatal outcome due to aNEN (Kirkegaard *et al*. 1981).

The 5-year OS has been reported as high as 95%, related to the anatomical site of the primary lesion and the state of the histological margins following resection in one study of 53 aNENs when compared to NENs from other primary sites (Shaw & Canal 1989); multivariate analysis of 619 patients revealed that age, stage and location of the tumour in the appendix predicted survival, but it is of interest that patients with regional disease lived even longer compared to those with localised disease (Quaedvlieg *et al*. 2001) (Supplementary Table 7, see section on supplementary data given at the end of this article). A German multicentre observational study reported aNENs displaying a 5-year OS of 83.1% vs 49.2% for non-carcinoid tumours (Benedix *et al*. 2010). In addition, in a large series from the SEER database stratified by tumour size, the authors did not detect any significant difference in survival between patients who underwent RHC and those who underwent simple appendicectomy (Groth *et al*. 2011), and this was confirmed by a more recent study of the same database (Shaib *et al*. 2015), implying either that RHC does not affect the outcome or that RHC improves the outcome in patients with more severe disease. Another interesting point in this latter study is the fact that specific cancer survival rates could be calculated, as opposed to other databases collecting OS rates (Groth *et al*. 2011) (Supplementary Table 8, see section on supplementary data given at the end of this article).

Regarding tumour stage, the 5-year OS for localised lesions was 94%, for regional invasion 84.6%, and for distant metastases 33.7% (Modlin & Sandor 1997, Sandor & Modlin 1998), and these outcomes have been confirmed by the more recent analysis of the SEER documenting a

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5-year disease-specific survival of 93% for malignant aNENs (McCusker *et al*. 2002). High survival rates have been confirmed also in smaller cases series (Godwin 1975, Ahlberg *et al*. 1980, Sjoblom 1988), with only one patient dying from metastatic disease (Godwin 1975). In a more recent study from the SEER, an effort was made to assess OS in months and this was impossible (not reached) for localised and regional disease, while for distant disease the median OS was 32 (95% CI (CI), 13% not reached) (Shaib *et al*. 2015).

There are few reports on the recurrence of aNENs after a prolonged follow-up period. In a series of 64 young patients diagnosed when <40 years old and followed for 10–33 years after operation, only one recurrence was documented in 1 patient with a tumour >2 cm and local metastases (Svendsen & Bulow 1980). In a small series of seven patients, only one patient, with a tumour >2 cm with MAI and LN metastasis, who underwent a RHC, developed liver metastases 6 years after the operation but survived after a liver resection (Fornaro *et al*. 2007). Lung metastases were also reported 2 years after RHC in one patient with MAI (Safioleas *et al*. 2005).

Follow-up

The recent guidelines from ENETS do not provide any follow-up recommendations for patients submitted to simple appendicectomy (Pape *et al*. 2012). The same is true for cases treated with RHC in the presence of some additional risk factor but without documentation of LN involvement or any residual disease in the resected specimen. Thus, it would seem on current data that such patients do not need regular follow-up with the associated costs and patient anxiety. However, regular long-term follow-up is advisable (although mostly unproven in terms of published data) according to recent guidelines when LN involvement or other extra-appendiceal disease has been revealed after RHC, or in cases with a size between 1 and 2 cm and some additional risk factors such as MAI or localisation at the base but without completion RHC, or finally, in higher stages even after RHC (Pape *et al*. 2012).

During follow-up, measurement of biochemical markers, specifically CgA, has been suggested to be performed yearly. Despite the fact that no data support its validity in aNEN recurrence, this is the only biochemical marker consistently studied so far being raised in 80–100% of patients with NENs (Alexandraki *et al*. 2011, Grozinsky-Glasberg *et al*. 2013). Assessment of urinary 5-HIAA levels should be reserved for cases with clinical symptoms of the CS (Grozinsky-Glasberg *et al*. 2013). There are no data available regarding the need to perform subsequent imaging to identify residual disease, the appropriate imaging modality required or, indeed, the frequency of repeating the imaging and the duration of follow-up. In contrast, there is concern regarding cumulative radiation exposure considering the young age of the patients using regular CT scanning. Transabdominal US has not been validated in this setting but may also be an option considering the improvement and safety of this technique. SRI has not been particularly useful in these tumours, which are usually too small to be detected by this technique, although this may not necessarily apply to ^{68}Ga-octeotide PET imaging that needs to be studied in the future because it is not widely available at present. The role of colonoscopy also has not been established, particularly regarding the possibility of some co-morbidities.

Conclusions

Summarising, aNENs are rare neoplasms mainly occurring in young people with current guidelines based on consensus discussions but lacking information from formal controlled trials (Plockinger *et al*. 2008, Pape *et al*. 2012). They are well-differentiated NENs, mostly grade 1 (Ki-67 <2%) tumours that have an excellent prognosis and can usually be safely removed with no further surgical intervention. When aNENs are confined to the appendix, they rarely cause metastatic disease, but when they do spread, they tend to involve the lymphatic system, and consequently they metastasise to the regional LNs rather than to the liver in the first instance (MacGillivray *et al*. 1991, Dall'Igna *et al*. 2005, O'Donnell *et al*. 2007, Mullen & Savarese 2011). Appendiceal NENs with a tumour size <1 cm rarely metastasise (<3%), whereas the risk of metastatic spread to either the LN or the liver is considerably higher in lesions >2 cm (30–60%) (Moertel *et al*. 1987, Gouzi *et al*. 1993).

At the time of diagnosis, we would recommend clinical examination and laboratory investigations with CgA, CT and/or MR imaging studies, but SRI will depend on the expertise and choice of individual units (Kaltsas *et al*. 2004). Data regarding prophylactic RHC are limited. For tumours >2 cm, or with positive pathological features, RHC is indicated (Sutton *et al*. 2003, Alexandraki *et al*. 2011). For tumours in the size range if 1–2 cm, previously characterised as of indeterminate risk, we believe it is reasonable to recommend RHC if at least one other risk factor is present (Grozinsky-Glasberg *et al*. 2013).

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Moreover, MAI at any depth without the limitation of 3 mm should be considered as a risk factor of more aggressive tumour behaviour. In terms of follow-up, in our opinion, for either the low-risk tumours (<1 cm in the largest diameter, no MAI presence, location at the tip or intermediate part of the appendix, low Ki-67 and no other extension) or the higher risk when the RHC shows no evidence of LN or other evidence of disease, no further follow-up may be indicated. When there is residual or additional evidence of disease following RHC, perhaps a safe strategy would be to perform yearly abdominal MRI scanning together with blood CgA, at least initially; we cannot on present data recommend the length of such follow-up. We emphasise that these are suggestions

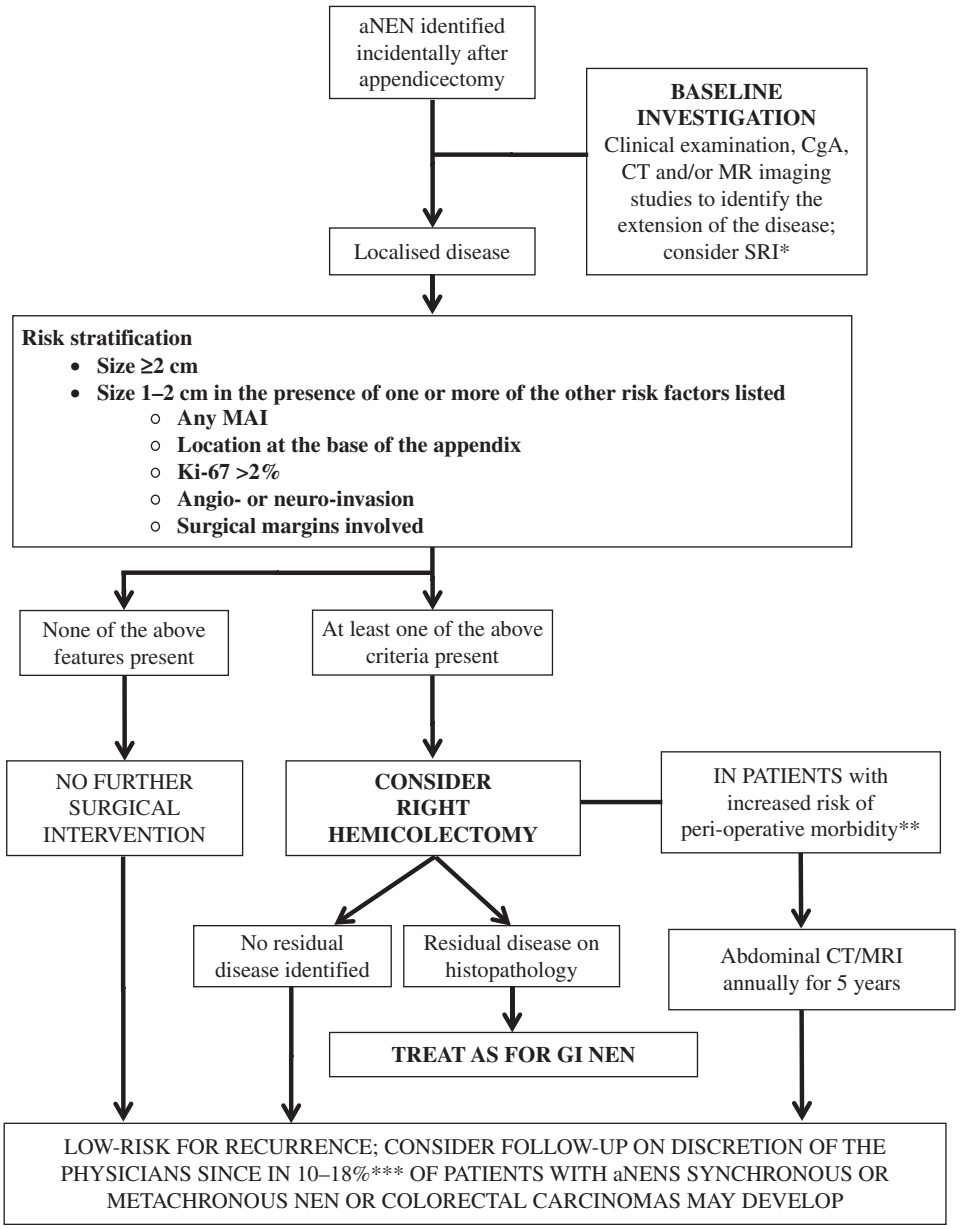

Figure 3

Therapeutic and follow-up algorithm for appendiceal neuroendocrine neoplasms incidentally found after appendicectomy for acute appendicitis or other abdominal or gynaecological procedures. aNENs, appendiceal neuroendocrine neoplasms; MAI, mesoappendiceal fat invasion; MRI, magnetic resonance imaging; NEN, neuroendocrine neoplasm; SRI, somatostatin receptor imaging; US, ultrasound scan. *SRI will depend on the expertise and choice of individual units due to the lack of evidence. **Patients who cannot be submitted to surgical procedures because of co-morbidities or who are unwilling to undergo operation. ***Bucher *et al.* 2004, Connor *et al.* 1998, Modlin *et al.* 2003, Modlin & Sandor 1997.

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based on current evidence, which emphasise our own recommendations, and may be subject to modification over time (Fig. 3).

Further research should be conducted by national and international collaboration, focusing on factors that predict metastatic behaviour. The recently published studies have the bias of very selective populations often with aggressive disease, as well as the unselected oncological population that usually present already extensive disease; such databases may be biased to more malignant disease and exclude patients with limited disease who may never be registered. Larger prospective studies focusing only on the aNENs may determine the prevalence of residual disease after appendicectomy in case of aNENs and the imaging and biochemical indices, which might predict the necessity of an invasive surgical treatment such as RHC. Larger series and more data may allow the establishment of criteria for recognising different risk groups of patients and consequently defining different guidelines for treatment.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-15-0310.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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