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Epidemiology and management of neuroendocrine neoplasms of unknown origin: an overview

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Abstract

Background: Neuroendocrine neoplasms (NEN) are rare tumors, mainly located in the lungs, pancreas or gastrointestinal tract. In some NENs the origin remains unidentified. They are referred to as cancer of unknown primary (CUP). Since only 9–14% of NENs are CUP, data about prognosis and therapy is scarce. Therefore, this paper aims to summarize the current knowledge on patients with CUP-NENs.
Methods: This analysis is a literature review, including the following databases, PubMed and Google Scholar, using the keywords neuroendocrine tumor, cancer of unknown origin, unknown primary, CUP, epidemiology, definition, therapy guidelines, survival. In all, 47 articles were selected and included.
Results: The available literature indicated that the median age of onset was higher in CUP compared to NENs of known origin. CUP had a comparatively higher rate of poorly differentiated neoplasia. The recommended imaging modality was computed tomography (CT), complemented by positron emission tomography (PET)/CT, using ^{68}Gallium-labeled somatostatin analogues (^{68}Ga DOTATOC, DOTANOC or DOTATATE PET/CT). Surgical resection was suggested as first-line therapy. Other treatment options included chemotherapy, somatostatin analogues, molecular therapy and radiotherapy. Compared to NENs of known origin, CUP were associated with a worse prognosis.
Conclusion: The current data suggest that CUP-NEN are frequently associated with older age and higher grade compared to patients with known-origin NENs. This reflected a worse prognosis for CUP-NENs.

Keywords
Diagnostic modalities · Cancer of unknown primary · Literature review · Demographics · Treatment · Survival

Introduction

Neuroendocrine neoplasms (NEN) are a rare and heterogeneous group of tumors which have their origin in neuroendocrine cells [1]. Identical to their origins, NENs are able to synthesize and secrete hormones and are characterized by the overexpression of specific peptide hormone receptors on the cell surface [2].

NENs are classified into well-differentiated and poorly differentiated. Differentiation thereby refers to how similar the tumor cells are to the normal healthy cells, measured by the mitotic count and Ki-67 index—a nuclear protein marker associated with cellular proliferation rate. Aggressiveness is determined on the basis of various parameters. These include the number of mitoses per unit area of tumor and the Ki-67 index, both of which represent the proliferation rate of the tumor. Another parameter is the presence of necrosis. Accordingly, NENS are classified into grades G1 or 2 if they are well differentiated and have a Ki-67 index be-

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Table 1 Overview of reported proportion of CUP in NEN

Authors	Time of observation (year)	Proportion of NEN-CUP (%)
Yao et al. [46]	1973–2004	13
Taal and Visser [7]	1989–1996	12
Korse et al. [47]	1990–2010	7.2
Begum et al. [3]	1990–2011	12.7
Du et al. [48]	1991–2013	10.8
Hauso et al. [11]	1993–2004	11–14
Begum et al. [14]	2000–2012	16
Garcia-Carbonero et al. [49]	2001–2008	9
Ploeckinger et al. [44]	2004–2007	13.6
Faggiano et al. [17]	2004–2007	4
Chauhan et al. [50]	2005–2015	7.6
Kollár et al. [51]	2008–2015	6

CUP cancer of unknown primary, *NEN* neuroendocrine neoplasms

low 3 or 20%. Meanwhile, tumors with a Ki-67% index above 20% are categorized as neuroendocrine tumors (NET) if they are well differentiated, and neuroendocrine carcinoma (NEC) if they are poorly differentiated [2–4]. In general, the classification into grades is not only important for the prognosis, but also has an impact on the therapeutic approach [5].

NENs can arise in various organs, but most frequently manifest in the lungs or gastrointestinal tract [6]. Nevertheless, there are patients in whom a NEN is diagnosed histologically but the origin of the primary tumor cannot be identified. These tumors are also referred to as cancer of unknown primary (CUP). Although there is a growing amount of research on CUP, the topic is comparatively poorly studied. This article, therefore, aims to summarize the currently available knowledge including demographic variables such as age and gender as well as diagnostic modalities, therapeutic modalities and overall survival.

Methods

Different databases were searched for this purpose, namely PubMed and Google Scholar. Several keywords were used to find suitable studies, i.e. neuroendocrine tumor, cancer of unknown origin, unknown primary, CUP, epidemiology, definition, therapy guidelines, survival. In addition, the reference list of important reports was screened for additional information. The time frame of the published paper was between 2000 and 2021. The focus was on the epidemiology, management (diagnosis and therapy) and survival of CUP patients. A total of 47 articles were included. Thereof, 18 articles were included in the section "Epidemiology", five in "Classification and Differentiation", 21 in "Diagnostic Procedures", eight in "Medical Treatment" and six in "Survival".

Results

Epidemiology

NENs are a relatively rare disease and represent only 0.5% of all malignancies. Thus the incidence of NENs is around 2/100,000 [7]. Epidemiological data suggest that the incidence has considerably increased in recent years [8]. There is no clear gender-related incidence, with different studies reporting conflicting results [9–11]. However, many authors suspect a higher incidence among women [10, 11]. Taken together, the incidence of NEN probably lies between 2 and 4.5/100,000, with a nearly equally distribution between male and female patients.

For CUP within NEN cohorts, rates from 4 to 16% of NEN are reported (**Table 1**). Other demographic variables are summarized in **Table 2**. A typical CUP-NEN patient is 56–72 years old without a clear gender preference.

Classification and differentiation

About 10% of the CUP-NEN were classified as well-differentiated low-grade tumors. However, among the remaining 90%, the majority was poorly differentiated [12]. A similar conclusion was reached in the publication by Stoyianni et al. [13]. In their data set from Ioannina University Hospital (single center CUP-NEN series), considerably more poorly differentiated neoplasms (71.4%) than well-differentiated neoplasms (28.6%) were reported. However, this is inconsistent with the study by Begum et al. [14] in which 63% of CUP-NEN patients were classified as WHO grade G1 or G2. This result is similar to another study by Begum et al. [3], in which 63% of CUP-NEN patients were diagnosed with G1, 10% with G2 and 27% with G3 neoplasms. Nevertheless, at 36%, CUP-NEN patients were considerably more likely to have a Ki-67 index of > 20% compared to NEN patients with known primary (16%).

Diagnostic procedures

The diagnosis of NEN as well as the search for the location of the primary in CUP involves several steps, as shown in **Fig. 1**. A characteristic neuroendocrine marker associated with NENs is chromogranin A (CgA), which can confirm neuroendocrine differentiation [15]. Although CgA is helpful in the follow-up but less so in diagnosing NENs, it provides no information about the primary location [16]. Therefore, the main challenge in CUP-NENs is to find the primary tumor. Some patients present with a functioning syndrome (26% of CUP-NEN, [17]) that can provide information about the primary using biochemical markers. One example thereof is the carcinoid syndrome which occurs in approximately 19% of NEN [18]. In this case, the symptoms occur secondary to an often very small tumor located in the small intestine associated with elevated levels of 5-hydroxyindoleacetic acid (5-HIAA) [19]. In ileum NENs, 5-HIAA is typically elevated, usually when liver metastases are present. In contrast, if the tumor is in the colon, rectum, or lung, levels are usually inconspicuous. Measurement of 5-HIAA is also not recommended for suspected NEN of the pancreas [20, 21].

The diagnosis of CUP in NENs is most often established in a patient with multiple metastasis associated with a significant tumor burden and the histological assessment is performed from a metastatic lesion [22]. Sometimes, immunohistochemistry

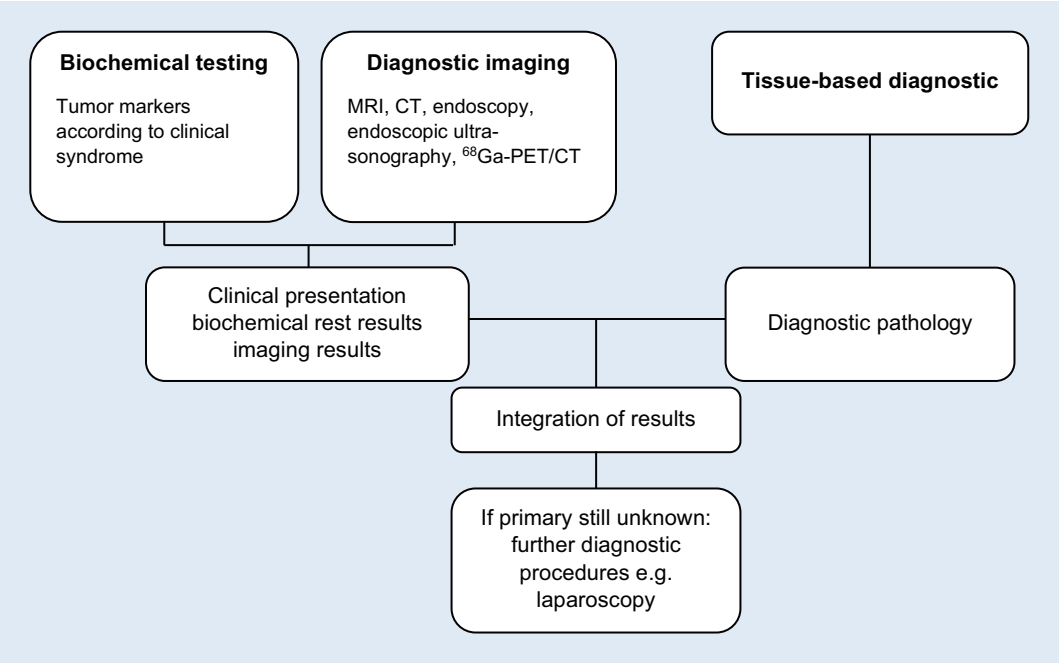

Fig. 1 ◀ Adapted diagnostic algorithm proposed by Hendifar et al. [22]. According to them, ^{68}Ga-positron emission tomography/computed tomography (^{68}Ga-PET/CT) should be considered if there is biochemical or clinical evidence of a neuroendocrine tumor but the primary cannot be found by using OctreoScan. However, the superiority of ^{68}Ga-PET/CT was demonstrated and therefore recommended instead of OctreoScan [26, 29, 30]. Diagnostic modalities were further expanded with endoscopy and endoscopic ultrasonography as well as laparoscopy [19, 35]

can help to further identify the location of the origin of the primary tumor, particularly in well-differentiated tumors. There are various immunohistochemical markers mentioned in the literature that could give an indication of origin (**Table 3**). Sangoi et al. [23] report, for example, that expression of PAX8 can distinguish pancreatic from ileal and pulmonary NENs. Other proposed markers are thyroid transcription factor 1 (TTF1) and caudal type homeobox 2 (CDX2) with TTF1 typically present in pulmonary and CDX2 in appendiceal as well as colonic tumors [24]. The diagnostic value of CDX2 has also been highlighted by Erickson et al. [25], who described CDX2 as a useful marker to identify CUP-NEN originating mainly from the small intestine. Immunohistochemistry yields overlapping results and does not provide a 100% sensitivity and specificity [15].

Conventional and functional imaging play an essential role to establish the tumor burden and—if possible—the primary site of origin [12]. Conventional imaging includes magnetic resonance imaging (MRI) and contrast enhanced computed tomography (CT) [26]. Other diagnostic options include endoscopy and endoscopic ultrasound. For example, upper gastrointestinal endoscopy is mainly used when a duodenal or gastric origin is suspected [19]. Endoscopic ultrasonography, on the other hand, shows a high detection rate in NEN of pancreatic origin and can therefore be used if pancreatic NEN is suspected [19, 27].

Imaging techniques, collectively referred to as functional imaging, are based on targeting the somatostatin receptors in differentiated NENs using nowadays mainly positron emitting radioisotopes such as gallium linked to octreotide in differentiated NEN [26]. In undifferentiated NENs, mainly 18F-fluoro-2-deoxyglucose positron emission tomography in combination with CT (18F-FDG PET/CT) is used for staging [28].

The currently best available functional imaging modality is ^{68}Ga-PET/CT which replaced the somatostatin receptor scintigraphy (OctreoScan, Mallinckrodt Pharmaceuticals, United Kingdom) due to the improved sensitivity, the shorten investigation time and the lower radiation burden [26, 29–31]. Therefore, its use is also recommended for the search of the primary tumor in CUP-NEN [32, 33]. Currently, there are three DOTA-coupled peptides available: DOTANOC, DOTATOC and DOTATATE [34].

Another approach is suggested by Wang et al. [35]. They argue that surgical exploration is useful for liver metastases to localize the concealed primary tumor and remove them at the same time. In this context, the primaries were mainly small and could mostly be localized in the small intestine. A similar conclusion was reached by Begum et al. [3]. They recommend open exploration after exhaustion of diagnostic possibilities to localize the primary tumor.

Medical treatment

If the primary tumor site can be localized through diagnostics, the therapy is determined by the primary tumor. For localized NENs, the treatment of choice is complete surgical resection. If the primary tumor cannot be found, the differentiation and grade of the metastasis is crucial for the therapeutic strategy. Even if the primary tumor cannot be found, resection plays an important role and is one of the first-line therapies for well to moderately differentiated metastases [12]. This is also supported by the study of Begum et al. [14], which showed that resection was an independent predictor of improved survival. Other treatment modalities include treatment with somatostatin analogues (SSA), such as Octreotide (Sandostatin® LAR®, Novartis, Basel, Switzerland) and Lanreotide (Somatuline Autogel®, Future Health Pharma GmbH, Wetzikon, Switzerland), approved to treat functioning and non-functioning NENs which are somato-

Table 2 Overview of demographic variables

Authors	Sample size[a]	NEN[b]	Age[c]: total (male/female)	Sex[d] (male)	CUP[b]	Age[c]: total (male/female)	Sex[d] (male)
Levi et al. [52]	433	433 (100%)	–	195 (45.0%)	–	–	–
Hemminki and Li [10]	5184	5184 (100%)	– (61/55)	2394 (46.2%)	–	–	–
Yao et al. [46]	35,618	20,886 (87%)	63	17,004 (48%)	4752 (13%)	–	–
Ploeckinger et al. [44]	1263	1263 (100%)	57 (59/56)	651 (51.5%)	172 (13.6%)	58 (60/56)	90 (52.3%)
Faggiano et al. [17]	820	820 (100%)	60.0	392 (48%)	36 (4.3%)	61.2	21 (58%)
Korse et al. [47]	47,808	47,808 (100%)	– (68/64)	29,700 (62%)	3418 (7.2%)	– (69/69)	–
Begum et al. [3]	261	228 (87.3%)	55.9*	1:1	33 (12.7%)	63.8*	1:0.95
Stoyianni et al. [13]	15	–	–	–	15 (100%)	68.5	8 (57.1%)
Begum et al. [14]	243	205 (84%)	56*	1:1	38 (16%)	65*	1.4:1
Hallet et al. [8]	5619	5619 (100%)	60.9*	2784 (49.5%)	–	–	–
Riihimäki et al. [42]	7334	7334 (100%)	60 (61/59)	3204 (44%)	795 (9%)	69 (67/72)	375 (47.2%)
Kollar et al. [9]	1063	1063 (100%)	61	559 (53%)	–	–	–

CUP cancer of unknown primary, *NEN* neuroendocrine neoplasms
[a]Data reported as numbers, *N*
[b]If the sample size is equal to the total sample, only those data were available. If differentiation was made between NEN and CUP, this can be seen by the subsamples
[c]Values are medians. If marked with * it refers to a mean value
[d]Data reported as numbers, *N* (%) or ratios (male:female) if no other data was available

Table 3 Histopathological markers

Localisation of NEN	Marker
Pancreas	CDX2 Isl-1 NESP-55 PAX6, PAX8 PDX1 PR
Small intestine	CDX2
Duodenum	PAX6, PAX8
Ileum	Serotonin
Appendix	Serotonin
Rectum	Isl-1 PAX6, PAX8
Bronchi	Ck7 TTF1

Markers used to localize the primary in NEN adapted from Berner et al. [16, p. 565]
NEN neuroendocrine neoplasms, *CDX2* caudal type homeobox 2, *Ck7* cytokeratin 7, *Isl-1* ISL LIM homeobox 1, *NESP-55* neuroendocrine secretory protein 55, *PAX* paired box protein, *PDX1* pancreatic and duodenal homeobox 1, *PR* Progesterone receptor, *TTF1* thyroid transcription factor 1

statin receptor subtype 2 (SSTR2) positive [36, 37]. In addition, peptide receptor radionuclide therapy (PRRT) can be considered. PRRT is a systemic treatment. Its principle of action is again based on the presence of SSTR2 on the NENs. These allow the radionucleotides to target/enter the tumor cells [38]. In this regard, PRRT is used for unresectable or metastatic, well to moderately differentiated NEN with in vivo proof of overexpressed SSTR2 as evidenced by a high uptake on 68Ga-DOTA-OC PET/CT [39, 40]. Newer molecular therapies such as sunitinib or everolimus may also be used. If the disease affects only the liver, methods such as local-ablative techniques, chemo- or radioembolization should be considered, regardless of the differentiation of the tumor [12].

Resection should also be considered for poorly differentiated metastases, combined with chemotherapy and possibly radiotherapy. If the tumor is inoperable, chemotherapy in combination with radiation can be considered. For poorly differentiated metastatic CUPs a platinum-based chemotherapy with etoposide is used analogue to the scheme for small cell lung cancer [12, 41].

Survival

Patients with CUP-NEN have a worse prognosis compared to patients with a known primary NEN. This is not only the case in patients with NEN but with tumors in general. Riihimäki et al. [42] showed that the median survival of patients with unknown primary of any tumor type was 3 months. In addition, compared to other patients with any metastatic tumors, risk of death was increased. Considering CUP in NENs, median survival has been reported to be 15.5 months. Again, survival of patients with CUP was shown to be shorter (11 months) compared to other patients (19 months) with metastatic NEN of known origin [43]. This is also supported by the study of Faggiano et al. [17], which demonstrated a significant decrease in survival probability with CUP in NENs compared to other NENs with known origin. Begum et al. [14] were able to identify various risk factors for survival in CUP-NENs. Survival was improved by young age, low WHO performance score, low WHO grade, low number of metastases, treatment by surgery and no need for chemotherapy.

As can be seen in **Table 4**, very few studies investigated survival with CUP in NEN. However, it can be summarized that the prognosis of CUPs in NENs is worse. Nevertheless, in CUP-NENs there are 15–20% of patients that have less aggressive tumors which can be treated and stabilized [12].

Discussion

In CUP-NENs, the data is inconsistent in terms of gender, with perhaps slightly more male patients suffering from CUP-NEN [13, 14]. Nevertheless, a recent study found that more women (52.8%) than men

Table 4 Overview of survival

Authors	CUP in general[a]	Survival (months)	NEN[b]	Metastatic NEN[b]	Survival (months)	CUP in NEN[b]	Survival (months)
Yao et al. [46]	–	–	35,097	–	75	–	–
Stoyianni et al. [13]	–	–	15	–	–	15	15.5
Hemminki et al. [53]	7730	3	–	–	–	–	–
Riihimäki et al. [42]	2881	3	–	–	–	–	–
Riihimäki et al. [43]	–	–	7334	1842 (25.1%)	19	795 (9%)	11

Sample size reported as numbers, *N* (%). Survival time is presented as median
CUP cancer of unknown primary, *NEN* neuroendocrine neoplasms
[a]Meaning any tumors with unknown primary, not specific in NEN. Values represent sample size as numbers, *N*
[b]Values represent sample size as numbers, *N*

(47.2%) presented with a CUP [43]. Unlike the other reported studies investigating CUPs in NENs [13, 14], this study included a substantially larger sample. Interestingly, the literature indicates that slightly more women develop NENs with known primary [10, 11]. More studies are needed to make a conclusive statement in terms of gender ratio.

For CUPs in NENs, a median age of 68.5 years at diagnosis was determined by Stoyianni et al. [13]. Begum et al. [14] were able to identify a similar median age of onset (69 years), which was consistent with the study by Riihimäki et al. [43]. Hence, the age at diagnosis date seems to be higher than for NEN with known primary [14, 43]. According to a large study with 5619 NEN cases from Canada, the mean age at diagnosis was 60.9 years in patients with known origin of NEN [8]. This is consistent with the publication by Riihimäki et al. [43], which reported a median age of 60 years in NEN with known origin. This study should be specifically mentioned as it examined the age of onset in NEN with known primary tumor and CUP separately in the same cohort. In this study, CUP-NEN patients were on average 9 years older at the time of diagnosis. A significant difference in the mean age could also been shown in the cohort examined by Begum et al. [3], with CUP-NEN patients being older at the time of diagnosis. One explanation for the difference in age could be that CUP-NEN patients are diagnosed in a more advanced state as indicated by the usually higher tumor load.

There is no consensus in the current literature regarding the grading distribution at the time of diagnosis of CUP-NENs. Polish et al. [12] claim that the majority of CUP-NEN can be classified as high-grade tumors. This was confirmed by the data from Stoyianni et al. [13], with 71.4% poorly differentiated neoplasms. Nevertheless, the aforementioned study examined data between 1999 and 2009. Furthermore, the sample consisted of only 15 patients diagnosed with CUP-NEN. This is in contrast to the research of Begum et al. [14] with 38 patients surveyed from 2000 to 2012. Thereby, 63% of CUP patients were classified as WHO grade G1 or G2. It may be possible that more tumors with lower grade are detected nowadays due to better diagnostics as well as an increased awareness. Improved detection is also implicated by Hallet et al. [8] as an explanation for the observed increased incidence of NEN with known and unknown primary. This implies, in turn, that there should be less CUPs in NENs over the years if detection of tumors and therefore the primaries had improved. A hint in favor of this hypothesis can be seen in **Table 1**, with higher rates of CUPs in studied NEN populations in older studies compared to more recent data. Although a tendency can be recognized, this statement cannot be conclusively clarified, since the studies were mainly retrospective and examined different populations. Moreover, some data seem to be contradictory, for example the study by Ploeckinger et al. [44].

In terms of imaging modalities, there is a wide range of diagnostic options. CT or MRI is often recommended as the first modality [12]. Endoscopic modalities such as endoscopy or endoscopic ultrasound may be used when an origin in the gastrointestinal tract is suspected. The use of endoscopic ultrasound is particularly recommended for a presumed pancreatic origin, showing high sensitivity and specificity in this context, and also allows further cytological investigation by fine needle aspiration [19, 27]. Molecular imaging such as somatostatin-receptor imaging is suggested. ^{68}Ga-PET/CT is the method of choice in the work-up of CUP-NENs since sensitivity, specificity and radiation exposure is in favor of ^{68}Ga-DOTATOC PET/CT compared to the scintigraphic approach (OctreoScan, Mallinckrodt Pharmaceuticals, United Kingdom) [26, 29–31]. Using ^{68}Ga-DOTANOC or DOTATOC PET/CT, the primary tumor was detected in 45–59% of patients [31, 33], resulting in a change of management in 20% of the cases [32]. Therefore, ^{68}Ga-PET/CT is recommended when there is clinical evidence of a NEN but its location cannot be found using conventional imaging modalities.

For the diagnosis of CUPs in NEN and determination of the site of origin, tumor markers can be of help. CgA is a sensitive marker for NENs in general but is not useful in identifying the origin of CUP NENs [15, 16]. Moreover, 5-HIAA is often assessed as a marker for NEN. It is increased in ileal NEN, but it must be considered that levels can be elevated by medications as well as diet, which can lead to false-positive findings [21]. In addition to the biochemical markers, immunohistochemical analysis can be used. PAX8, for example, is proposed to distinguish pancreatic from ileal and pulmonary NENs since it was positive in 74% of pancreatic but in none of ileal or pulmonary NENs [23]. Yet, PAX8 also has a considerable overlap, including appendiceal, gastric, rectal, and above all duodenal NENs, as well as in 27% of solid-pseudopapillary pancreatic neoplasms. Thus, PAX8 alone cannot indi-

cate the origin of the tissue if it is positive. On the other hand, a negative sample cannot exclude an origin with complete certainty. Furthermore, only well-differentiated neoplasms with known localization were studied. Also, the aforementioned markers TTF1 and CDX2 are each positive in only 43% of pulmonary and 86% of appendicular or colonic NEN, respectively. In poorly differentiated neoplasms, 50% of non-pulmonary tumors were also TTF1 positive. This indicates that the use of tumor markers in predicting the origin is more difficult in poorly differentiated neoplasms [24].

As in all NENs, surgery can be an option for CUP-NEN if morbidity is acceptable [12]. The importance of surgical resection in NEN is also underlined by the findings of Kollar et al. [9]. Since CUP-NEN patients often present with advanced disease, it may not be possible to remove the whole tumor bulk. As an alternative method, biotherapy can be considered if functional imaging is consistent with overexpression of SSTR2. Somatostatin analogues such as Octreotide LAR (Sandostatin® LAR®, Novartis, Switzerland) or Lanreotide (Somatuline Autogel®, Future Health Pharma GmbH, Switzerland) are approved. They are critical for the control of secreting NENs and for morphological stabilization [36, 37, 45]. In patients with high-grade gastroenteropancreatic CUP-NENs, another commonly used form of therapy is chemotherapy, for example with carboplatin in combination with etoposide. The efficacy of platinum-based chemotherapies in this combination has been demonstrated, for example objective responses could be documented in 52% and stable disease in 24% of patients [41]. PRRT is another therapeutic option frequently used in NEN, including in CUP-NEN. Its use could lead to a reduction in targeted lesions of up to 86%, but a clinically significant effect of PRRT was demonstrated only in SSTR2 positive, mainly differentiated NENs [39]. Taken together, therapeutic management in CUP-NEN is not different from the management of NENs in general. There is no data comparing therapeutic efficacy in patients with CUP-NEN and NEN in general with the aforementioned modalities.

There is data indicating that the survival in metastatic disease is better in NENs with known primary compared to CUP-NENs [17, 43]. This is consistent with data from any kind of cancer with unknown origin where survival is only 3 months [42]. In terms of NEN, the study of Stoyianni et al. [13] reported a median survival of 15.5 months in CUP-NEN patients. Thus, as Polish et al. [12] has already described, the prognosis for CUP in NEN seems to be better compared with other malignant neoplasms of unknown origin [13]. In comparison to NENs in general, however, the prognosis is markedly worse. Notably, it has been shown that the median overall survival in NEN patients with known origin is 75 months [46]. It should be considered that the aforementioned study did not distinguish between metastatic and non-metastatic disease. To make a valid comparison between NEN with known primary tumor and without, the tumor burden including metastasis should be taken in account. Still, a possible explanation for the noticeable difference in survival may be the expected high rate of poorly differentiated neoplasms at diagnosis, which was described before [12, 13]. According to Yao et al. [46], a higher tumor grade is associated with a worse prognosis. Another possible hypothesis could be that poorly differentiated neoplasms show a rapid growth of symptomatic metastases leading to a diagnosis although the primary tumor is still comparatively small. This would be consistent with the study of Begum et al. [14], in which a Ki-67 index of > 20% was detected in 36% of CUP patients compared to only 16% of NEN patients with known primary tumor.

A limitation of this review is the fact that there are only small studies available for CUP-NEN patients and the management of NEN patients is constantly changing taking in account new diagnostic and therapeutic options. Furthermore, the availability of methods for the diagnostic and therapeutic approach often depends on local competence and availability. Therefore, it is difficult to make general statements. Future studies are needed to investigate the optimal management of CUP in large-scale trials. Even more fundamentally, the understanding of the basics of CUP such as sex differences or grading at diagnosis should be improved using large patient samples.

Conclusion

In terms of demographic variables, there are no clear gender disparities. There is perhaps a slight male preponderance that remains to be confirmed. The median age at diagnosis for CUP-NEN patients compared to NEN patients with known primary tends to be higher. Date on differentiation of neoplasms at diagnosis is controversial, but it is likely that CUP-NEN patients suffer from less differentiated NENs than NEN patients with tumors of known origin. In the diagnostic workup, there is a clear recommendation to favor the use of CT in combination with ^{68}Ga-DOTATOC to detect the location of the primary tumor in CUP-NEN. On the other hand, when searching for the primary, it is important to include the clinical and biochemical markers as well as the immunohistological assessment of a biopsy to possibly specify the origin of the NEN. Like in NEN of known origin, the same therapeutic modalities are used, including surgery, local ablative methods, biotherapy, chemotherapy, targeted therapy and PRRT. The sequence of these modalities is ill-defined and depends on availability and expertise. Compared to NENs with known primary tumor, median survival in CUP-NEN is markedly shorter, consistent with the higher rate of poorly differentiated NENs and the older age of CUP-NEN patients. Further studies based on large-scale trials are needed to understand the fundamentals of CUP in NEN and to improve the management thereof.

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Declarations

Conflict of interest. L. Rhonheimer, J. Refardt and E. Christ declare that they have no competing interests.

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studies mentioned were in accordance with the ethical standards indicated in each case.

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Zusammenfassung

Epidemiologie und Management neuroendokriner Neoplasien unbekannter Herkunft – ein Überblick

Hintergrund: Neuroendokrine Neoplasien (NEN) sind seltene Tumoren, die hauptsächlich in der Lunge, der Bauchspeicheldrüse oder dem Magen-Darm-Trakt auftreten. Bei einigen NEN bleibt der Ursprung unbekannt. Sie werden als Karzinome unbekannter Herkunft („cancer of unknown primary" [CUP]) bezeichnet. Da es sich nur bei 9–14 % der NEN um CUP handelt, liegen nur wenige Daten zur Prognose und Therapie vor. Daher soll in diesem Beitrag der aktuelle Wissensstand hinsichtlich Patienten mit CUP-NEN zusammengefasst werden.
Methoden: Bei dieser Analyse handelt es sich um eine Literaturübersicht, für die die Datenbanken PubMed und Google Scholar unter Verwendung der Schlüsselwörter neuroendocrine tumor, cancer of unknown origin, unknown primary, CUP, epidemiology, definition, therapy guidelines und survival durchsucht wurden. Es wurden 47 Artikel ausgewählt und eingeschlossen.
Ergebnisse: Aus der verfügbaren Literatur geht hervor, dass das mittlere Erkrankungsalter bei CUP im Vergleich zu NEN bekannten Ursprungs höher ist. CUP wiesen eine vergleichsweise höhere Rate an schlecht differenzierten Neoplasien auf. Die empfohlene bildgebende Methode war die Computertomographie (CT), ergänzt um eine Positronenemissionstomographie(PET)/CT mit ^{68}Galium-markierten Somatostatinanaloga (^{68}Ga-DOTATOC-, ^{68}Ga-DOTANOC- oder ^{68}Ga-DOTATATE-PET/CT). Als Erstlinientherapie wurde die chirurgische Resektion empfohlen. Weitere Behandlungsoptionen waren Chemotherapie, Somatostatinanaloga, molekulare Therapie und Strahlentherapie. CUP waren im Vergleich zu NEN bekannten Ursprungs mit einer schlechteren Prognose verbunden.
Schlussfolgerung: Die aktuellen Daten deuten darauf hin, dass CUP-NEN im Vergleich zu NEN bekannten Ursprungs häufig mit einem höheren Alter und einem höheren Grad verbunden sind. Dies spiegelt sich in einer schlechteren Prognose für CUP-NEN wider.

Schlüsselwörter
Diagnostische Verfahren · Krebserkrankung unbekannter Herkunft · Literaturübersicht · Demografie · Therapie · Überleben