International Variation in Diagnostic and Treatment Guidelines for Carcinoma Unknown Primary

S.J.M. Kok
Comprehensive Cancer Organization the Netherlands, Department of Research, Utrecht, The Netherlands
Email:c.schroten@iknl.nl
H.W.M. van Laarhoven
Academic Medical Center, Department of Medical Oncology, Amsterdam, The Netherlands
Email:h.vanlaarhoven@amc.uva.nl
V.E.P.P. Lemmens
Comprehensive Cancer Organization the Netherlands, Department of Research, Utrecht, The Netherlands
Email:v.lemmens@iknl.nl
C. Schroten
Comprehensive Cancer Organization the Netherlands, Department of Research, Utrecht, The Netherlands
Email:c.schroten@iknl.nl

ABSTRACT

Guidelines intend to provide the medical professional with a set of recommendations on the best standards of care. For carcinoma of unknown primary, a heterogeneous group of metastatic malignancies for which the site of origin is not detected, several guidelines are internationally available. Because each guideline is developed by a different committee with their own point of view, these guidelines might advise differently regarding diagnostic and treatment strategies for patients with a malignancy of unknown origin.

Via an internet search, using the terms “guideline(s)”, “CUP” and “carcinoma unknown primary”, four guidelines were identified: the NCCN guideline from the USA, the SEOM guideline from Spain, the NICE guideline from the United Kingdom and the European guideline (ESMO), based in Switzerland. These guidelines and our national guideline used in The Netherlands, were compared and an overview was made of the differences and consistencies of the advised diagnostic, treatment and follow-up strategies.

Of the five compared guidelines, only one guideline (NICE) mainly focuses on the logistics with regard to patient care while other guidelines focus more on the diagnostic strategies to identify the primary tumor site. The described diagnostics sometimes show overlap but frequently differ on the various recommended diagnostic tools to identify the site of tumor origin such as PET, CT, MRI, IHC markers, ultrasound and endo-, colo-, colposcopy. For the treatment of patients with CUP the guidelines often refer to the guideline of the suspected primary tumor site. Only one guideline (NICE) generally refers to a multidisciplinary team to discuss the best possible treatment for the patient.

Numerous differences between the CUP guidelines were observed. These differences in diagnostic strategies, and the different diagnostic tools used, result in divergent perceptions regarding the definition of the term “carcinoma unknown primary” and makes comparison of incidence rates, survival times and treatment strategies challenging. International collaboration regarding evidence based guideline development might be of benefit for medical professionals and their patients.

Keywords- carcinoma unknown primary, guidelines, oncology, diagnostics

1. INTRODUCTION

Carcinoma of unknown primary (CUP) represents a heterogeneous group of metastatic malignancies of which the site of origin is not detected after a careful review of the complete clinical history, physical examination, routine laboratory testing, imaging and histological results. The global incidence of CUP is estimated to be about 3% of all new diagnosed cancers.[16] Lymph nodes, liver, lungs and bones are the most common metastatic sites involved and over 50% of patients present with multiple metastatic sites at diagnosis.[4, 8, 10] In general, patients diagnosed with CUP have a poor prognosis and a short survival, only 20% survives beyond one year.[23] The prognosis with regard to survival time is more optimistic for patients with metastasis in lymph nodes only, compared to those patients diagnosed with metastases in internal organs.[9, 11] In some patients the combination of clinical presentation and CUP workout findings leads to a provisional diagnosis. Identification of a probable site of origin might implicate a more specific treatment, which is assumed to positively affect overall survival time.[16-19]

For that reason, guidelines can support medical professionals in their search of the (probable) tumor site of origin and subsequent treatment. As a starting point, guidelines classify CUPs into five major subtypes after routine evaluation with light microscopy. Well- or moderately differentiated adenocarcinomas are the most frequent (60%), followed by poorly differentiated or undifferentiated adenocarcinomas (29%), squamous cell carcinomas (SCC, 5%), poorly differentiated malignant neoplasms (5%) and neuroendocrine tumors of unknown primary (1%).[8, 12, 22] Using these subtypes, more detailed investigations can be performed in an attempt to identify the primary site of origin.

Worldwide, different evidence based guidelines are available for CUP. In this article we provide an overview for medical professionals on the differences and consistencies between CUP guidelines available on the internet and written in English, and our national guideline used in The Netherlands. An overview is given of the different strategies with respect to primary tumor site identification as well as differences in treatment and advice about CUP management.

2. METHODS

Comparison of guidelines. An internet search, using the Google search engine, was performed on the term "guideline" in combination with "CUP" or "carcinoma unknown primary". The guidelines retrieved and the guideline used in The Netherlands (Oncoline), are depicted in Table 1.[5, 7, 13-15] Three guidelines claim to be completely evidence-based, in contrast to the Spanish (SEOM) and USA (NCCN) guidelines that are partly evidence-based, partly consensus-based. For all of the above mentioned guidelines we compared the recommended diagnostic strategy, treatment and follow-up.

The reported comparison is divided into an initial recommended strategy for the identification of the primary tumor site, and a secondary strategy based on the probable primary site of tumor origin. A schematic overview is made to visualize the differences and the consistencies between the guidelines regarding the diagnostic tools used as well as the recommended treatment options.

3. RESULTS

In general, the topics addressed in the compared guidelines are the organization of patient care, initial diagnostics, additional diagnostics and treatment.

3.1 Organization

With regard to organizational recommendations on patient care, only the NICE guideline advices on this subject. In summary, the establishment of a CUP team by every hospital with a cancer center or unit and the assignment of a CUP specialist nurse or key worker is advised. Preferably, patients with CUP should be referred to, and assessed by, the CUP team within two weeks. Furthermore, the formation of a CUP network multidisciplinary team (MDT) is advised. The abovementioned professionals should ensure, whenever appropriate, that CUP patients and their caretakers are given the proper information, advice and support about diagnosis, treatment, palliative care, spiritual and psychosocial support, symptom management, end-of-life consultations and hospice care. In Table 2 the organizational recommendations are shown per guideline.

3.2 Initial diagnostic strategy

With regard to the initial diagnostic strategy to identify the primary tumor site, all guidelines agree that a complete history and physical examination should be performed. These examinations include head and neck, breast, pelvic and rectal investigation. Furthermore, routine laboratory investigations, computerized tomography (CT) thorax and histopathological investigations using specific tumor markers are recommended. However, guidelines differ with respect to X-thorax, endoscopy, positron emission tomography (PET) scan, PET/CT scan and fecal blood analysis. The SEOM guideline and the Dutch guideline Oncoline state that PET should be included into the standard diagnostic procedures in case of CUP. Moreover, histopathological examination differs on the determination of S-100, HMB45, CD45/LCA, PLAP, thyroglobulin, calcitonin, NSB, chromogranin, syntaptophysin, PSA, AFP, OCT4, HCG, vimentin, desmentin, ER and TTF-1 expression levels. The Oncoline and NICE guidelines do not describe the initial diagnostics in detail (Table 2A and 2B).

Table1. Overview of guidelines on carcinoma unknown primary

Guideline organization	Version	Year	Latest Update	Planned Revision	Country	Internet address
Oncoline, The Netherlands Cancer Registry	1.0	2012		unknown	The Netherlands	www.oncoline.nl
European Society for Medical Oncology		2011	May 2011	unknown	Switzerland	www.esmo.org
National Comprehensive Cancer Network	1.0	2015	15-9-2014		USA	www.nccn.org
National Institute of Health and Care Excellence	1.0	2010	May 2013	None, Feb 2014 placed on static list	UK	www.nice.org.uk
Spanish Society of Medical Oncology		2014	15-9-2014	unknown	Spain	www.seom.org

Table 2A. Initial diagnostic strategy to identify the primary tumor site

Guideline	Diagnostic													
	History examination	Physical examination												
		Head/Neck	Breast	Pelvic	Rectal	X thorax	CT thorax	Endoscopy	CT abdomen	CT pelvis	PET	PET/CT	Routine laboratory tests (blood, urinalysis)	Fecal blood
Oncoline	+	+	+	+	+	+	+		+	+		+	+	
ESMO	+	+	+	+	+		+		+	+			+	
NICE	+	+	+	+	+		+	+	+	+			+	
SEOM	+	+	+	+	+		+	+	+	+	+*		+	+
NCCN	+	+	+	+	+		+	+	+	+			+	+

* : PET in case of suspected primary pulmonary tumor site

3.3 Secondary diagnostic strategy

3.3.1 Patients with suspicion of a primary head/neck carcinoma

The European (ESMO) and Spanish (SEOM) guidelines recommend 2-deoxy-2-(^{18}F)fluoro-D-glucose-PET/CT (FGD-PET/CT) for patients with suspicion of head/neck carcinoma based on the initial diagnostic outcomes (Table 3). Endoscopy, biopsies (blind/targeted) were not advised by ESMO guidelines, in contrast to the guidelines of Oncoline, NICE and SEOM. Furthermore, in case of metastatic presentation in the cervical nodes, the NCCN guideline refers to the head and neck guidelines of occult primary. Yet, the Oncoline and ESMO guidelines suggest the use of a head and neck CT scan and the NICE and SEOM guidelines recommend the use of FDG-PET. Oncoline is the only guideline that recommends imaging studies of the entire body in case there are SCC in the lower 1/3 region of the neck, and with adenocarcinomas independent of their localization. Furthermore, histological biopsies are not advised because of the risk of graft metastases. Only if two cytological punctions are inconclusive, a biopsy needs to be performed, preferably a lymph node excision rather than an incision biopsy.

3.3.2 Patients with suspicion of a breast cancer

Patients with axillary node metastasis, for whom the initial diagnostic strategy (Table 2) points towards a possible primary tumor site in the breast, should be additionally examined using mammography. When mammography does not identify a primary site in the breast a magnetic resonance imaging (MRI) scan is suggested. Besides the MRI scan, the guidelines of NICE and NCCN suggest a role for ultrasound examination. Furthermore, all compared guidelines recommend the detection of the estrogen receptor (ER) by IHC on metastatic tissue. Nevertheless, dissimilarities were observed with regard to IHC on the progesterone receptor (PR), the human epidermal growth factor receptor 2 (Her2Neu), carcinoembryonic antigen (CEA), mammoglobin, gross cystic disease fluid protein (GCDFp15), and the usage of the Cancer antigen 15-3 (Ca 15.3) marker (Table 3A).

3.3.3 Patients with suspicion of a lung cancer

Patients for whom the initial diagnostic strategy points towards possible primary lung cancer should be investigated accordingly (Table 3A). Possible lung cancer can present as a neuroendocrine tumor (NET) or as an adenocarcinoma. The additional diagnostic advice to identify the primary tumor varies among the guidelines from bronchoscopy/targeted biopsies/ washings and video-assisted thoracic surgery (VATS) (in case of a negative bronchoscopy) for adenocarcinoma, and octreoscan and plasma chromogranin A determination for NET. The NCCN guideline is the least specific about additional diagnostics for this patient group and refers to their neuroendocrine tumor guidelines.

3.3.4 Patients with liver metastases or with suspicion of a colon carcinoma

For patients presenting with liver metastases most guidelines advise endoscopy or colonoscopy in combination with the determination of serum alpha fetoprotein (AFP) or cancer antigen 19-9 (CA19-9) levels

if a pancreatic or biliary tract primary tumor is suspected (Table 3B). When the colon is suspected to harbor the primary tumor site (with or without liver metastases) based on the initial diagnostic outcomes, the diagnostic tools of choice are endoscopy and the detection of CEA expression by IHC according the majority of the guidelines. Both the guidelines of Oncoline and NICE state that CEA is not useful as a serum marker for colon carcinoma due to its low specificity. Only the NICE guideline recommends peritoneal disease tissue sample histology in case of ascites.

3.3.5 Patients with suspicion of a ovarian carcinoma

The additional diagnostics, for patients suspected to have an ovarian carcinoma as a primary tumor site, hardly vary regarding the advised IHC markers Wilms Tumor 1 (WT-1) and Cancer antigen-125 (CA-125). Yet, the NICE guideline emphasizes the limited test specificity of serum CA-125 measurement, and for this reason CA-125 test results should be interpreted with care. Recommendations regarding diagnostic laparoscopy, ultrasound/CT and gynecologic consultation differ among the guidelines (Table 3C). Ultrasound/CT is advised for women with peritonitis carcinomatosa and increased CA-125 level by Oncoline. If the primary site could not be detected in the ovaria or tubae eventually a diagnostic laparoscopy is recommended. This recommendation is also made by the SEOM guideline, however, without previous examination using ultrasound. The NICE guideline is the only guideline which advises tissue sampling for histological examination in patients presenting with ascites and peritoneal metastases, if technically possible.

Table 2B. Initial diagnostic strategy to identify the primary tumor site

	Organisation			Diagnostic: Histopathological examination (tissue)											
Guideline	**CUP specialist / Key worker**	**CUP team**	**MDT**	**CK 7**	**CK20**	**S-100, HMB45**	**CD45/LCA**	**PLAP**	**Thyroglobulin, calcitonin**	**NSB, chromogranin, syntaptophysin**	**PSA**	**AFP, OCT4, HCG**	**Vimentin, desmentin**	**ER**	**TTF-1**
Oncoline				+	+				+		+			+	
ESMO				+	+	+	+	+	+	+	+	+			
NICE	+	+	+	+	+			+			+			+	+
SEOM				+	+	+	+						+		
NCCN				+	+	+	+	+							

Abbreviations: CK7: cytokeratin 7; CK20: cytokeratin 20; S-100: S-100 protein; HMB45: human melanoma black 45; LCA, leucocyte common antigen; PLAP, placental alkalin phosphatase; NSB: nonspecific binding; PSA, prostate specific antigen; ER, estrogen receptor; AFP, A-fetoprotein; hCG, human chorionic gonadotropin; TTF-1, thyroid transcription factor 1; OCT4: octamer binding transcription factor 4; HCG: human chorionic gonadotropin

Table 3A. Recommended additional diagnostics to identify the primary tumor site

	Suspected for primary tumor site: Head/Neck							
	Visual inspection	**Endoscopy**		**PET/ CT**	**PET**	**MRI**	**Targeted biopsies**	**Blind biopsies**
Guideline	**Face/scalp/ auditory meatus**	**Ear/nose/throat/ pharynx/larynx/ cervical esophagus**	**Pulmonary area**			**Head/neck region**		
Oncoline	+	+				+a	+	+b
ESMO				+				
NICE		+			+c			
SEOM		+	+	+				
NCCN								

	Suspected for primary tumor site									
	Breast									
				IHC						
Guideline	Mammography	MRI	Ultrasound	ER	PR	GCDFP-15	Her2	CEA	Mammoglobin	Ca15.3
Oncoline	+	+		+	+		+			
ESMO	+	+		+	+	+		+	+	
NICE	+	+	+	+	+		+			
SEOM	+	+		+	+	+	+	+	+	+
NCCN	+	+	+	+			+	+		

	Suspected for primary tumor site					
	Lung					
	Adenocarcinoma			*Neuroendocrine tumor*		
Guideline	Bronchoscopy	VATS	Targeted biopsies	Octreoscan	PET/CT scan	Plasma chromogranin A
Oncoline	+	+	+d	+		
ESMO				+		+
NICE	+e	+f				
SEOM				+	+	+g
NCCN						

a: FDG-PET or MRI; b: 'Blind"biopsies of different locations like base of tongue or nasopharynx might be taken into consideration; c: NICE: when endoscopy doesn't lead to visible tumor and only if radical treatment is an option; d: dependent on result of bronchoscopy; e: combined with biopsy, brushings and washings; f: only with negative bronchoscopy and when percutaneous biopsy is considered inappropriate; g: Chromogranin A + sinaptofisine + CD56 + PGP9 (protein gene product 9)

ER: estrogen receptor; PR: progesterone receptor; GCDFP-15: gross cystic disease fluid protein 15; CEA: carcinoembryonic antigen; Her2: human epidermal growth factor receptor 2; Ca15.3: cancer antigen 15.3; PSA: prostate specific antigen; VATS: video-assisted thoracic surgery

Table 3B. Recommended additional diagnostics to identify the primary tumor site

	Suspected for primary tumor site/ metastatic site						
	Liver metastasis				Colon		
	Endoscopy	Colonoscopy	Serum levels		Endoscopy	IHC	Histology
Guideline	GI		AFP	CA 19-9	GI	CEA	Tissue
Oncoline		+	+				
ESMO	+				+		+
NICE			+	+	+h		
SEOM	+	+	+		+	+	
NCCN	+		+	+		+	

	Ovarian					
	Gynaecologic consultation	Ultrasound/CT	Serum levels	Diagnostic laparoscopy	IHC	
Guideline	Invasive pelvic examination	Abdomen	CA-125	Abdomen	WT-1	CA-125
Oncoline	+	+	+	+	+	+
ESMO					+	
NICE			+			+
SEOM	+		+	+	+	+
NCCN	+				+	+

	Suspected for primary tumor site/metastatic site				
	Prostate		Germ cell		
	Serum levels	Detailed urological investigation	Ultrasound testis	Serum levels	Isochrome i12p
Guideline	PSA			AFP and β-HCG	
Oncoline	+		+	+	
ESMO	+			+	
NICE	+		+	+	
SEOM	+	+	+	+	+
NCCN	+		+k	+	

***h**: Only in case of suspicion for GI primary tumor; k : Only in case of elevated AFP and β -HCG;*

Table 3C. Recommended additional diagnostics to identify the primary tumor site

	Suspected for primary tumor site/metastatic site					
	Inguinal					
	Targeted physical examination	Colposcopy	Proctoscopy	PET/CT	Endoscopy pulmonary	IHC
Guideline						CA-125
Oncoline	+	+		+		
ESMO						
NICE						+
SEOM	+				+	
NCCN	+	+	+	+		

3.3.6 Patients with suspicion of a prostate cancer

Prostate serum antigen (PSA) determination is recommended by all guidelines. Yet, Oncoline and NICE recommend PSA determination for all male patients, while NCCN advises this for men >40 years of age with an adenocarcinoma or carcinoma NOS (without metastases in liver or brain) and the SEOM and ESMO guideline recommend serum PSA determination in men with bone metastasis regardless of age (Table 3B).

3.3.7 Patients with suspicion of a germ cell tumor

The diagnostics tools advised by the compared guidelines are limited to ultrasound of the testis as well as IHC (Table 3C). However, the ESMO guideline only advises determination of serum AFP and human chorionic gonadotropin (β-HCG).

The NCCN only recommends testicular ultrasound in case of elevated serum levels of AFP and HCG in men with a mediastinal or retroperitoneal mass. Furthermore, the SEOM notes that the detection of isochrome i12p can support primary tumor site diagnosis. And differentiation between testicular germ cell cancer and non-small cell lung cancer may require further analyses.

3.3.8 Additional diagnostic strategies for patients with inguinal metastases

The NICE guideline does not specifically address patients with inguinal metastases. Inguinal node involvement can occur in women with presentations compatible with ovarian cancer. In those patients, tumor marker CA-125 should be measured, despite its limited specificity. The diagnostic tools advised for this patient group vary between PET, and the combination PET/CT, Endoscopy, IHC, colposcopy and targeted physical examination (Table 3C). According to the Oncoline guideline, in patients with isolated inguinal metastases, especially from SCC, targeted physical examination should be used to rule out anal- and penis carcinoma, as well as vulva- and vaginal carcinoma.

For the latter, additional imaging studies (colposcopy) might be useful. For resectable malignancies, FDG-PET/CT might be considered. The SEOM guideline advises to perform pulmonary endoscopic evaluation and PET in patients with inguinal lymphadenopathy with squamous histology. Anorectal, urological and gynecological examination is indicated. According to the NCCN guideline, the recommended examination of patients with SCC in the inguinal nodes should exist of CT scans of the abdomen and pelvis, perineal and lower extremity examination, gynecologic oncology consult and anal endoscopy.

3.3.9 Additional diagnostic strategies for patients with solitary metastasis

The PET scan, with or without CT, is the diagnostic tool of choice for operable patients with a solitary metastasis by almost all guidelines (Table 3C). Furthermore, colonoscopy for patients with a solitary metastasis located in the liver is suggested by the Oncoline guideline. Then again, the NICE guideline states that "inappropriate investigation of a tumor may reduce radical treatment outcome" and referral to an MDT is advised.

3.4 Recommended treatment options

3.4.1 Treatment strategies based on suspected primary tumor site or metastatic site

Patients with clinical and/or laboratory characteristics of a specific malignancy should receive the appropriate treatment aimed at this specific malignancy. In Table 4, the recommended treatments are shown by the suspected primary tumor site or, if no suspected primary could be identified, by type of metastases. The NCCN guideline does not advise in detail on treatment, instead it frequently refers to other guidelines for patients with a known primary tumor site. The NICE guideline is also not very specific with regard to treatment options for CUP patients and regularly advises to refer patients to a specific MDT.

The multidisciplinary approach of a treatment is preferable according to the NICE guideline, as well as a multidisciplinary approach regarding palliative and supportive care. The guidelines of Oncoline, ESMO and SEOM are more detailed regarding treatment options, which mainly vary between surgery, chemotherapy and radiotherapy, depending on the suspected primary tumor site or metastatic site and the performance status (PS) of the patient. For CUP patients with multiple metastatic sites, inclusion of the patient into a clinical trial is preferred with special attention to symptom control, consideration of chemotherapy on an individual basis and specialized approaches, such as targeted therapies and novel forms of radiation therapy. Treatment goals are directed toward symptom control and providing the best quality of life possible, especially in patients with multiple metastatic sites. Likewise, the ESMO guideline recommends to evaluate response after two or three chemotherapy cycles by individually adequate tests, to weigh quality of life issues against treatment-related toxicity. Follow-up frequency for patients with either active disease or limited metastatic disease in remission should be determined by clinical need.

Table 4A. Treatment options for patients with carcinoma unknown primary

	Oncoline	**ESMO**	**NICE**	**SEOM**	**NCCN**
	Brain metastases				
Surgery				x (up till 3 metastases)	
Chemotherapy	x (trial)		x (trial)		
Refer to guideline					Central nervous system cancers
Refer to …			Neuro-oncology MDT		
Other:		NS		Patients with limited remove metastasis: whole brain radiotherapy or stereotactic radiosurgery	
	Liver metastases				
Surgery	x			x	x
Chemotherapy				x	x

Radiotherapy	x				
Refer to guideline					
Other:		NS	NS	Chemoembolization, radiofrequency ablation (RFA), percutaneous alcohol injections	In case of irresectable: guideline hepatobiliary cancers
	Inguinal metastases				
Surgery	x (LN)	x (LN)		x (LN)	x (LN)
Chemotherapy	x	x		x	x
Radiotherapy				x	x
Refer to …			MDT		
Other:		NS	Specialist surgeon		
	Solitary metastases				
Surgery	x	x		x	x
Chemotherapy					x
Radiotherapy	x	x		x	
Refer to …			MDT		
Other:		Systemic therapy NS	Radical local treatment NS		

Table 4B. Treatment options for patients with carcinoma unknown primary

	Oncoline	**ESMO**	**NICE**	**SEOM**	**NCCN**
	Suspected for head/neck carcinoma				
Surgery	x (bilateral tonsillectomy, removal of cervical lymph nodes)	x (neck dissection)		x (node dissection)	
Chemotherapy				x	
Radiotherapy				x	
Refer to guideline				Primary head and neck cancer	Primary head and neck cancer
Other:		Chemoradiation	Head/Neck MDT		
	Suspected for breast cancer, axillary lymph node metastases				
Surgery		x (LN + mastectomy)		x (LN + mastectomy)	
Radiotherapy				x	
Refer to guideline	Breast cancer	Breast cancer	Breast cancer	Breast cancer stage II-III	Breast cancer
Refer to …			Breast cancer MDT		
Other:		Chemohormonotherapy	Clincial trials		
	Suspected for NET				
Surgery		x			
Chemotherapy		x (streptozocin + 5-FU)			
Hormonal therapy		x (somatostatin analogs)			
Targetted therapy		x (sunitinib, everolimus)			

Refer to guideline	Small-cell NET: Small-cell carcinoma of lung				Neuroendocrine tumors
Other:	High-grade large-cell NET: treatment as high-grade NET of lung.	Table 3A applies to well differentiated NET. Poorly differentiated neuroendocrine carcinoma of unknown primary: therapy as poorly differentiated NET with a known primary .	NS	NS	
	Adenocarcinoma metastases presenting as lung nodules				
Surgery				x	x
Chemotherapy				x	x
Refer to guideline					Non-small cell lung cancer
Refer to …			MDT		
	Suspected for coloncarcinoma				
Surgery	x				
Chemotherapy				x	
Radiotherapy	x				

Table 4C Treatment options for patients with carcinoma unknown primary

	Oncoline	**ESMO**	**NICE**	**SEOM**	**NCCN**
	Suspected for ovarian carcinoma				
Surgery		x (debulking)		x	
Chemotherapy		x		x	
Refer to guideline	Ovarian cancer	Ovarian cancer for patients with optimal debulking		Ovarian cancer and Non-small cell lung cancer depending on age and location of metastasis	Ovarian cancer and Non-small cell lung cancer depending on age and location of metastasis
Other:			NS		
	Suspected for prostate cancer				
Surgery					x
Chemotherapy					
Radiotherapy		x			x
Hormonal therapy		x		x	
Refer to guideline	Prostate cancer	Prostate cancer			
	Bone metastases				
Surgery	x			x	x
Chemotherapy					
Radiotherapy	x			x	x
Hormonal therapy					
Refer to …			MDT		
Refer to guideline					

Other:	Surgery only when vital structures like myelum are in danger,		Radical local treatment NS		Surgery only in patients with good PS and potential for fracture in a weight-bearing area
	Suspected for germ-cell tumor				
Chemotherapy		x		x (age 40-50 years)	
Refer to guideline	Germ cell			Germ cell and Non-small cell lung cancer depending on age	Testicular cancer or Ovarian cancer and Non-small cell lung cancer depending on gender and age

4. CONCLUSIONS

This is the first study comparing guidelines for carcinoma of primary unknown origin (CUP). We observed considerable heterogeneity in the recommended diagnostic and therapeutic strategies. Where some guidelines provide more general strategies, others include detailed diagnostic and treatment strategies with regard to the suspected site of tumor origin. In general, clinical guidelines are important to provide specialists and multidisciplinary teams with directives on diagnosis and treatment, especially for uncommon tumor types, to provide patients with the best possible care.

From the compared guidelines, the UK guideline (NICE), is the only one to focus on recommendations for the general organization of CUP patient care, rather than on detailed information on the diagnostic strategy for identifying the primary site of origin. The observed differences between the diagnostic strategies of the guidelines, and the different diagnostic tools used, implicate divergent perceptions regarding the definition of the term “carcinoma unknown primary”. A tumor can only be categorized as “carcinoma unknown primary”, if a primary tumor cannot be identified after performing certain diagnostic tests. As described, the initial diagnostic strategy might lead to suspicion of a specific primary tumor site, after which more detailed secondary diagnostic investigations can be performed. Consequently, when those investigations lead to the identification of a primary tumor site, the diagnosis of CUP disappears because it is replaced by an alternative diagnosis. The initial diagnostic strategies to identify the primary tumor site are in general similar across the compared guidelines. However, the additional strategy, which is based on the outcome of the initial diagnostic strategy, differs among all guidelines in recommended imaging tools and histopathological examinations. It is therefore not unthinkable that a CUP identified according one guideline might not be considered a CUP when identified according to another guideline. Furthermore, differences and consistencies between the guidelines could partly be explained by the age of the guidelines, while one guideline is just renewed the other is almost ready for revision. Also, the methods by which the guidelines are developed might also be of influence: the outcomes are influenced by the initial questions on which the guidelines are based, the literature included in the evidence-based guidelines, the persons involved in selecting and assessing the literature, and the translation of conclusions found in literature to recommendations included in the guidelines for diagnosis and treatment.[1, 2, 6, 20, 21] Since the definition of CUP depends on the diagnostic strategy that is followed, CUP incidence rates, treatments and survival times between countries are difficult to compare. Preferably, a worldwide agreement on the procedures leading to the diagnosis “carcinoma of unknown primary” would be implemented to facilitate medical treatment and care as well as scientific research. Determining the focused minimal diagnostic tools per metastasis localization to identify the primary tumor site, which could be adapted to fit local medical and cultural habits, might be helpful regarding the definition of the term “carcinoma unknown primary”.

Patients with clinical and/or laboratory characteristics of a specific treatable malignancy should receive the appropriate treatment aimed at that specific malignancy.[24] Many CUP guidelines refer to the guideline of the suspected primary tumor site, however, most of these guidelines are not equipped with a section which focuses specifically on patients with an occult primary tumor site. Therefore, patients with an unknown primary tumor site are treated as if they have the malignancy of suspicion, however, leaving specialists in uncertainty about specific additional actions to be taken in case of CUP. Yet, one should always keep in mind that apparent metastases could be uncommon primary tumors. Besides the patient group that is considered to be treatable, there are also patients that do not belong to a specific treatable subgroup and should receive the best supportive care with regard to their performance status according to the guidelines. Details on ‘the best supportive care' are missing in all of the guidelines, referral to another guideline or organization is suggested by Oncoline and NICE. The Netherlands as well as the UK both developed guidelines for palliative and psychosocial care. These are

umbrella guidelines, for all types of cancer and not specific for CUP. Since the uncertainty with regard to their disease is immense for all CUP patients, extra attention for palliative and psychosocial care should be embedded into the (CUP) guidelines.[3]

Since there are no effective treatments for CUP patients and many of the metastases are reported to be resistant for chemotherapy, more effective treatment modalities are needed. Participation in clinical trials is recommended for CUP patients with adequate performance status, however the survival time of patients suffering from CUP is limited.[19-23] With regard to survival, unfavorable features including poor PS, male gender, adenocarcinoma with involvement of multiple organs, non-papillary malignant ascites (adenocarcinoma), multiple cerebral metastases (adenocarcinoma or SCC) and adenocarcinoma with multiple lung/pleural or bone lesions were related to poor prognosis. Unfortunately, at this moment models to predict survival for individual patients are not available.

In conclusion, the guidelines for CUP all describe strategies to identify the primary tumor site. The guidelines present an overlap with each other with regard to initial diagnostic strategies, but there are numerous differences between the compared guidelines with regard to secondary diagnostic strategy. Ideally, an international agreement on the procedures leading to the diagnosis “carcinoma of unknown primary” would be implemented to facilitate medical treatment and care as well as scientific research. The resulting universal guideline for CUP should be updated regularly, based on the outcomes of recent clinical trials and local medical and cultural habits,. Extra attention for palliative and psychosocial care should be embedded into the CUP guidelines. Furthermore, the development of a prediction model based on tumor markers and patient characteristics with regard to patient prognosis is desired.

ACKNOWLEDGEMENT

The authors thank drs. J.J.F. de Groot and drs. A.Y. Steutel for their critical reading and feedback.

Conflict of Interest

Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

[1] Abdelsattar ZM, Reames BN, et al. (2015) Critical evaluation of the scientific content in clinical practice guidelines. Cancer 121:783-789

[2] Berkman ND, Lohr KN, et al. (2014) Grading the strength of a body of evidence when assessing health care interventions: an EPC update. Journal of clinical epidemiology

[3] Boyland L, Davis C (2008) Patients' experiences of carcinoma of unknown primary site: dealing with uncertainty. Palliative medicine 22:177-183

[4] Chorost MI, Lee MC, et al. (2004) Unknown primary. Journal of surgical oncology 87:191-203

[5] Collado Martin R, Garcia Palomo A, et al. (2014) Clinical guideline SEOM: cancer of unknown primary site. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 16:1091-1097

[6] Djulbegovic B, Kumar A, et al. (2015) Quality of evidence is a key determinant for making a strong guidelines recommendation. Journal of clinical epidemiology

[7] Fizazi K, Greco FA, et al. (2011) Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 22 Suppl 6:vi64-68

[8] Hainsworth JD, Greco FA (1993) Treatment of patients with cancer of an unknown primary site. The New England journal of medicine 329:257-263

[9] Hemminki K, Bevier M, et al. (2012) Survival in cancer of unknown primary site: population-based analysis by site and histology. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 23:1854-1863

[10] Hess KR, Abbruzzese MC, et al. (1999) Classification and regression tree analysis of 1000 consecutive patients with unknown primary carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 5:3403-3410

[11] Kodaira M, Takahashi S, et al. (2010) Bone metastasis and poor performance status are prognostic factors for survival of carcinoma of unknown primary site in patients treated with systematic chemotherapy. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 21:1163-1167

[12] Moertel CG, Kvols LK, et al. (1991) Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 68:227-232

[13] NCCN (2015) Occult primary (Cancer of Unknown Primary [CUP]) Version 1.2015 [Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site]. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)

[14] NICE. (2010) Diagnosis and management of metastatic malignant disease of unknown primary origin. Full guideline. [Available at: http://www.nice.org.uk/nicemedia/live/13044/49864/49864.pdf.

[15] Oncoline (2012) Primaire tumor onbekend. Landelijke richtlijn, Versie 1.0 [Available at: http://www.oncoline.nl/primaire-tumor-onbekend].

[16] Pavlidis N, Briasoulis E, et al. (2003) Diagnostic and therapeutic management of cancer of an unknown primary. European journal of cancer 39:1990-2005

[17] Pavlidis N, Pentheroudakis G, et al. (2009) Cervical lymph node metastases of squamous cell carcinoma from an unknown primary site: a favourable prognosis subset of patients with CUP. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 11:340-348

[18] Pentheroudakis G, Lazaridis G, et al. (2010) Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. Breast cancer research and treatment 119:1-11

[19] Pentheroudakis G, Pavlidis N (2010) Serous papillary peritoneal carcinoma: unknown primary tumour, ovarian cancer counterpart or a distinct entity? A systematic review. Critical reviews in oncology/hematology 75:27-42

[20] Qaseem A, Forland F, et al. (2012) Guidelines International Network: toward international standards for clinical practice guidelines. Annals of internal medicine 156:525-531

[21] Reames BN, Krell RW, et al. (2013) Critical evaluation of oncology clinical practice guidelines. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31:2563-2568

[22] Spigel DR, Hainsworth JD, et al. (2009) Neuroendocrine carcinoma of unknown primary site. Seminars in oncology 36:52-59

[23] van de Wouw AJ, Janssen-Heijnen ML, et al. (2002) Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984-1992. European journal of cancer 38:409-413

[24] Varadhachary GR, Raber MN, et al. (2008) Carcinoma of unknown primary with a colon-cancer profile-changing paradigm and emerging definitions. The Lancet Oncology 9:596-599