REVIEW

Diagnosis and management of neck metastases from an unknown primary

Diagnosi e trattamento delle metastasi laterocervicali da sede primitiva ignota

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Key words

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Parole chiave

Sede primitiva ignota • Diagnosi • Chirurgia • Radioterapia

Summary

Neck lymph node metastases from occult primary constitute about 5%-10% of all patients with carcinoma of unknown primary site. Metastases in the upper and middle neck (levels I-II-III-V) are generally attributed to head and neck cancers, whereas the lower neck (level IV) involvement is often associated with primaries below the clavicles. Diagnostic procedures include a careful clinical evaluation and a fiberoptic endoscopic examination of the head and neck mucosa, biopsies from all suspicious sites or blindly from the sites of possible origin of the primary, computerized tomography scan, and magnetic resonance. The most frequent histological finding is Squamous Cell Carcinoma, particularly when the upper neck is involved. In these cases, a systematic tonsillectomy in the absence of suspicious lesions is discussed since up to 25% of primary tumours can be detected in this site. Thoracic, and abdominal primaries (especially from lung, oesophagus, stomach, ovary or pancreas) should be sought in the case of adenocarcinoma and involvement of the lower neck. Positron emission tomography with fluoro-2-deoxy-D-glucose allows detection of primary tumour in about 25% of cases, but this procedure is still considered investigational. Therapeutic approaches include surgery (neck dissection), with or without post-operative radiotherapy, radiotherapy alone and radiotherapy followed by surgery as reported by several guide-lines. In early stages (N1), neck dissection and radiotherapy seem to have similar efficacy, whereas more advanced cases (N2, N3) require combined approaches. The extent of radiotherapy (irradiation of bilateral neck and mucosa versus ipsilateral neck radiotherapy) remains debatable. A potential benefit from extensive radiotherapy should be weighed against its acute and late morbidity and difficulties in re-irradiation in the case of subsequent primary emergence. The role of other methods, such as chemotherapy and hyperthermia, remains to be determined.

Riassunto

Le metastasi laterocervicali costituiscono circa il 5-10% dei pazienti affetti da carcinoma da sede primitiva ignota (CUP). Il coinvolgimento dei linfonodi dei livelli medi e superiori del collo (I-II-III-V) è generalmente attribuito a neoplasie del distretto cervico facciale, mentre i livelli bassi (livello IV) sono spesso associati a neoplasie non di pertinenza del distretto cervico-facciale (a partenza da organi siti al di sotto della clavicola). L'iter diagnostico prevede una attenta valutazione clinica ed endoscopica del distretto cervico facciale, biopsie di tutte le aree sospette o a random dalle sedi di possibile origine e valutazione radiologica con tomografia computerizzata e risonanza magnetica. Il carcinoma spinocellulare è l'istologia più frequente, soprattutto quando sono coinvolti i livelli cervicali superiori. In questi casi, in assenza di lesioni sospette, taluni autori consigliano una tonsillectomia sistematica, in considerazione del fatto che nel 25% dei casi si riscontra la neoplasia primitiva in tale sede. L'adenocarcinoma, soprattutto se il linfonodo metastatico è al IV o V livello) potrebbe originare da una neoplasia tiroidea ovvero da una neoplasia primitiva toracica o addominale (in particolare polmone, esofago, stomaco, ovaio e pancreas). La tomografia ad emissione di positroni con fluoro-2-desossi-glucosio (PET) permette l'individuazione del primario in circa il 25% dei casi, ma riveste ancora un ruolo sperimentale. I diversi approcci terapeutici sono riportati nelle linee guida redatte dalle maggiori istituzioni cliniche e dalle società scientifiche: linfoadenectomia laterocervicale eventualmente seguita da radioterapia, radioterapia esclusiva oppure radioterapia seguita da chirurgia sono le strategie più utilizzate nelle varie situazioni cliniche. In stadi precoci (N1) lo svuotamento laterocervicale e la radioterapia sembrano avere gli stessi risultati, mentre in casi avanzati (N2, N3) è indispensabile un approccio combinato. L'estensione della radioterapia (irradiazione del collo e delle mucose bilateralmente ovvero una irradiazione del collo monolaterale) rimane oggetto di discussione. I vantaggi di una estesa irradiazione vanno messi a confronto con la morbidità acuta ed a distanza del trattamento stesso e con la difficoltà di una eventuale re-irradiazione qualora venisse evidenziata la neoplasia primitiva. Il ruolo di altre metodiche quali la chemioterapia e la ipertermia sono ancora oggetto di studio.

Introduction

Carcinoma of unknown primary site (CUP) represents a heterogeneous group of malignancies presenting with lymph node or distant metastases, for which diagnostic work-up fails to identify the site of origin [1]. CUP accounts for 5%-10% of all tumours and, as a result of recent improvement in imaging procedures, its number is decreasing [1-3]. Moreover, due to progress in immunopathology, more individualized histology-based therapeutic options have recently become available [1-3]. A substantial fraction of CUP patients includes cases with cervical lymph node metastases from unknown primary [4 5]. Squamous cell carcinoma (SCC) is the most common histotype, followed by adenocarcinoma, undifferentiated carcinoma and other malignancies (for example, lymphoma and melanoma) [6-9]. Patients with cervical metastases other than SCC follow different treatment guidelines and have different prognosis [10-12]. The management of cervical lymph node metastases from unknown primary remains a therapeutic challenge. Randomized trials are lacking. As far as concerns SCC, since they are characterized by loco-regional progression and relatively low risk of distant metastases, the priority is given to loco-regional control. Therefore, local modalities including surgery and radiotherapy remain cornerstones of treatment. Recently, the role of combined chemo-radiotherapy after surgery of Head and neck SCC with nodal metastases has been stressed [13-15]. Treatment of other malignancies depends on the histotype and site of origin. Published retrospective series include heterogeneous patient populations (with different histotypes, i.e., squamous cell, undifferentiated carcinoma and adenocarcinoma) [8 9 16-21] managed with various diagnostic and therapeutic procedures [8 11 18 19 21-25]. However, the recent publication of several relatively large series of patients allows for some conclusions to be drawn [7 16 26-29]. References for this review were identified by a comprehensive search of MEDLINE for the years 1990-2004 (with no language restriction). References were supplemented with relevant citations from older literature, from the reference list of retrieved papers, and from the official guidelines of the European Institute of Oncology and of several Scientific Societies found surfing the web [30-34]. Papers were selected on the basis of their relevance to the topic. Data presented in abstract form or non-English language articles were included wherever they added significant information.

Incidence

The incidence of cervical CUP varies between 2% and 9% of all head and neck cancers [8 9 35-37]. In the Danish national study, the annual incidence of cervical metastases of SCC from unknown primary was 0.34 cases/100,000/year, and has remained stable over the last 20 years [29]. In the same period, the number of new head and neck cancers has increased, suggesting that the proportion of CUP cases has diminished [29]. The most frequently involved nodal areas are level II, followed by level III, whereas levels I, IV and V are less frequent [6 29 38 39]. Unilateral lymph node involvement is more common; bilateral adenopathy is present in about 10% of patients [12 24 38]. In large series, the median nodal size was 5 cm (range 2-14 cm) [38] and there is an apparent prevalence of N2 cases [6 24 25 28 29]. Metastases in the upper and middle neck are generally attributed to cancers of the head and neck region, whereas metastases limited to the lower neck (supraclavicular area) are often associated with primary malignancies below the clavicles [8 22 36 40]. Many patients with exclusive low neck involvement are managed with palliative approaches [29]. Mean age at diagnosis varied in some series from 55 to 65 years, and younger median age in some series may partially be explained by the inclusion of undifferentiated tumours [6 7 21 25 27 28 35 39-41]. As in other head and neck carcinoma populations, the majority of patients are males [6 11 21 25 27-35 38-42]. The reported median interval between the first symptoms and diagnosis and/or referral to oncology clinic was approximately 3 months [6 39].

Diagnostic approaches

Diagnosis procedures should be aimed at clarifying the histology of the nodal metastases and detecting the primary.

History

Family and Personal history, including history of previous malignancy both in the head and neck, and elsewhere; history of previous radiation; history of a previous facial or cervical skin lesion that has disappeared; history of any upper aero-digestive tract related symptoms (sore throat, otalgia, hoarseness, dysphagia, hearing loss or epistaxis), and of previous operations (breast, abdomen, chest, etc.).

Clinical evaluation

Scrupulous physical and fiber-optic evaluation of the head and neck district including palpation of the oral cavity, oropharynx, and base of the tongue, and search for scars in the head and neck indicating previous surgery.

Examination of the neck, which includes site, size, mobility, and relationship of the node(s) to the adjacent structures.

Complete physical examination for abnormalities

elsewhere: breast, axilla, groins, testicles, abdomen. A fine needle aspiration for cytologic diagnosis (FNAC) is recommended if the above evaluation does not detect any primary. Repetitive non-diagnostic FNACs are an indication for an open biopsy, intra-operative histologic examination and possible neck dissection [18 28 43 44]. These procedures, performed by experienced specialists, allow detection of the primary in more than 50% of patients [45].

Imaging

Head and neck imaging includes computerized tomography scan (CT), and magnetic resonance imaging (MRI).

The thoracic (trachea, oesophagus and lung) and abdominal (liver, ovary, testis and prostate) primaries have to be excluded by chest and abdomen CT scan and endoscopic examinations (tracheo-broncoscopy, oesophago-gastroscopy, colonscopy). This is of particular relevance in patients with metastases to the left lower cervical (supraclavicular) lymph nodes.

The role of Positron Emitted Tomograohy (PET) is discussed [46-49]. PET scan has an overall staging accuracy of 69-78%, a positive predictive value of 56-83%, a negative predictive value of 75-86%, a sensitivity of 63-100% and a specificity of 90–94% [42 46 48]. With negative routine clinical examination, CT, and MRI, PET scan allows detection of primary tumours in 5-43% of patients [5 37 42 46 48-52]. Higher rates of primary tumour detection were observed if non-head and-neck CUP or histologies other than SCC were included in the analysis. In the series including exclusively head and neck SCC CUP, the detection rate did not exceed 25% [46]. The resolution of the PET scan is usually limited to 5 mm [46]. Tumours of the supraglottic region and Waldeyer's tonsillar ring are the most difficult to be diagnosed with FDG-PET [53]. This can be explained by the low tumour volume in small, superficial lesions, the presence of normal lymphoid tissues, and the accumulation of FDG secreted by salivary glands to saliva pools in the valleculae and pyriform sinuses [47 53]. Improved detection may probably be achieved with a 12-h pre-study fast, which diminishes salivary gland excretion and enhances FDG uptake in tumours [54]. All metastatic cervical lymph nodes detected by CT were confirmed by PET scan [42 51]. Ideally, biopsies should be performed after PET scan, since such a sequence allows for sampling of the areas suspected in PET and avoids false positive PET-scans at biopsy site. Apart from the detection of primary tumour, other potential advantages of PET include exclusion of other metastases, post-radiotherapy neck evaluation (selection of patients with residual disease) and subsequent monitoring [42 47 55-57].

Other diagnostic procedures

Recently, promising results have been reported with laser-induced fluorescence imaging performed in parallel to panendoscopy [57]. Another diagnostic method to identify the site of origin with higher sensibility is FDG-SPECT, however its usefulness is still debated [40 58].

Molecular assays

Some molecular assays have recently been proposed to differentiate the potential primary site. Detection of the Epstein-Barr virus (EBV) with the use of in situ hybridization in metastatic lymph nodes may suggest nasopharyngeal tumour [59]. Human Papilloma virus (HPV) detected by polymerase chain reaction may indicate oropharyngeal cancer [60]. Microsatellite mutation analysis of metastatic nodal tissue and samples of normal pharyngeal mucosa was also proposed [61]. Despite these encouraging results, little is known about the biology of CUP. It was hypothesized that in CUP the primary acquires a metastatic phenotype soon after transformation and remains small, either by inborn errors leading to involution of the primary, or due to extremely slow growth rate. Another postulated mechanism was inhibiting the growth of the primary by metastases [62]. Definitely, more studies are needed to evaluate the role of molecular investigations and to understand the biology of CUP.

Examination under general anaesthesia

When the primary is not dectected, an evaluation under general anaesthesia is mandatory. Usually biopsies are taken from all sites suspicious at the clinical and imaging evaluation, and blindly from the sites of possible origin of the primary, including base of tongue, tonsil or tonsillar fossa, pyriform sinus and nasopharynx on the lesion side [63]. Planned neck dissection to be performed. Another option is open biopsy [25 37], although an increased risk of distant metastases following this procedure has been suggested [15]. The detection rate with the use of CT scan is about 15-20% [64] and panendoscopy with biopsies can detect the primary in up to 65% of patients [40]. The most common sites of primary (82%) are tonsil and base of tongue [40]. Some patients present with synchronous primary tumours [40]. In the last few years, the incidence of occult primaries detected subsequently in the nasopharynx, hypopharynx, and supraglottic larynx has decreased [36]. This can reflect more effective primary detection of these lesions with the use of fiberoptic endoscopies and advanced radiographic methods [36 40]. In the case of nodal metastasis from SCC a systematic tonsillectomy, in the absence of suspicious lesions, is recommended by many Authors, since up to 25% of primary tumours are detected in this site [7 9 17 25 35 46 65-67]. The highest rate was observed in the case of involvement of subdigastric lymph nodes, followed by submandibular and midjugular nodes [25]. Some investigators limit recommen-

dation of tonsillectomy to cases with suspicious findings on physical examination and/or radiographic evaluation [40] or to the involvement of the afore-mentioned high-risk lymph nodes [25]. Only four cases of bilateral synchronous tonsillar cancer in CUP patients have been published in the literature [68]. On the other hand, a 10% rate of contralateral spread from occult tonsil lesions seems to justify bilateral diagnostic tonsillectomy [7 17 69]. Despite numerous studies, the optimal diagnostic algorithm in head and neck CUP has not yet been established; from our analysis of the literature and guidelines recommended by several Institutions and Scientific Societies, we summarise in Table I the diagnostic procedures for which there is consensus.

Management

Various therapeutic approaches are being employed for CUP, including surgery, and radiotherapy alone or combined treatment (surgery, radiotherapy and chemotherapy). The choice of the treatment schedule depends on the histology and on the stage of the disease.

Squamous cell carcinoma

Therapy includes surgery (biopsy and neck dissection) and radiotherapy. However, the optimal extent of surgery and radiotherapy is still controversial [9 19 21 70]. Some authors recommend only diagnostic surgical procedure followed by radiotherapy [29 71]. Many Authors suggest neck dissection (levels I-V) in patients with N1 disease without extracapsular extension and with no history of incisional or excisional biopsy, and postoperative irradiation in the case of a previous biopsy, extracapsular spread, and N2-N3 disease [26 27 38 46 72-78]. Salvage neck dissection is indicated in nodal relapses [29] or is performed routinely after irradiation (planned neck dissection) [40]. The majority of patients receive extensive bilateral neck irradiation including head and neck mucosa (pharyngeal axis) as a potential site of primary [6 7 16 28-29 39 79-81]. The curative radiotherapy dose to the mucosa varied in different series from 50 to 70 Gy [6 11 29 35 38 80], and to the neck from 59 to 70 Gy [6 8 11 29 80]. As in the head and neck cancer manage-

Table I. Diagnostic work-up (from the literature).

Clinical evaluation
Personal history, focusing on tumour history
Performance status, respiratory system and cardiovascular evaluation with ECG; additional exams at the discretion of the physician
Complete ENT clinical and fibrescopic evaluation, careful examination of surgical scars
Imaging
Chest X-ray, Thyroid and neck US
FNA biopsy (slides review if biopsed elsewhere)
Exams following cyto/histopathological diagnosis:
Squamous cell carcinoma or undifferentiated carcinoma
MRI/CT
PET-CT
Anti EBV antibodies evaluation (in case of undifferentiated carcinoma)
Physical examination under general anaesthesia, including inspection and palpation of the oral cavity, base of tongue, oropharynx and nasopharynx. Direct laryngoscopy and pharyngoscopy. Biopsy of any abnormal mucosa seen or palpated. If there are no visible or palpable abnormalities, and the FNA suggests squamous cell carcinoma or poorly differentiated malignancy, biopsy of sites of suspected primary depending on the position of the involved nodes. This usually includes biopsies of the nasopharynx, base of the tongue and pyriform sinus.
Adenocarcinoma
MRI/CT
PET-CT; PSA, CA125 e CEA assay. Liver enzymes and function tests (since nodal disease in the neck may be manifestation of metastatic disease from a primary site below the clavicle, in which case, metastatic liver disease may also be present).
Salivary glands, thyroid, lungs physical and imaging evaluation, mammography. CT scan of the abdomen and pelvis, and GI imaging or endoscopic studies may be in order depending on the location of the neck node, the patient's age, individual risk factors and the results of pelvic/rectal exams.
Lymphomas
Lymph node biopsy
Multidisciplinary discussion (Surgeons, Radiotherapists, Medical Oncologists) for planning treatment

ment, hyperfractionated radiotherapy was used in CUP patients, although its superiority over conventional irradiation remains to be established [38]. Another innovative strategy tested in CUP patients was the combination of radiotherapy and hyperthermia [80].
Inoperable neck disease is usually treated by radiotherapy alone [26 27 46 71].
A combination of chemotherapy and extensive irradiation was proposed by several Authors [8 82]. Platinum-based chemotherapy preceding radiotherapy is also recommended for N3 disease by the European Society of Medical Oncology (ESMO) [1]. Some investigators advocate chemotherapy for supraclavicular lymph node involvement [16] or for undifferentiated tumours [9]. However, according to the American Physician Data Query (PDQ) recommendations, both chemotherapy and hyperfractionated radiotherapy remain investigational approaches [63]. Indeed, in the review of Nieder et al. [46] no data were found to support the benefit of chemotherapy. Future investigation should be directed to the therapeutic approaches shown to be beneficial in locally advanced head and neck cancer, such as post-operative radiochemotherapy [83] or definitive concomitant radiochemotherapy for inoperable tumours [84 85].
Undifferentiated and the majority of patients receive extensive bilateral neck irradiation including pharyngeal mucosa [6 7 13 25 26 31 72]. The estimated actuarial risk of emergence of head and neck primary after extensive irradiation is up to 20% at 10 years [7 28]. In the majority of series, extensive radiotherapy resulted in reduced primary tumour occurrence [23-25 30 31 61 73-77]. In the large Danish study, the risk of loco-regional relapse after extensive radiotherapy was reduced twofold as compared to the ipsilateral therapy. This effect was mainly due to the reduction of neck recurrences [26]. The effectiveness of radiotherapy is illustrated by the fact that the risk of emergence of a primary lesion after extensive irradiation is similar to the occurrence of second tumour in a patient with overt head and neck cancer.

Poorly differentiated carcinoma

The most frequent possible site of origin is pharynx, particulalry nasopharynx. Treatment consists of radiotherapy to the neck and Waldeyer's ring including the nasopharynx. Neck dissection is reserved for residual disease. Consideration may be given to sparing the nasopharynx, when Anti EBV antibodies (IgA antibodies to viral capsid antigen and early antigen) are not elevated [86]. Doses and techniques of radiotherapy are those used for treatment of Undifferentiated Nasopharyngeal Carcinomas. Concomitant chemo-radiotherapy is indicated in the case of N2-N3 nodes.

Adenocarcinoma

Node located at level I-III could develop from a salivary gland tumour. In these cases, an excisional biopsy is indicated. If clinical and pathological evaluation cannot identify the source of the primary, there is consensus on neck dissection (levels I-V), including parotidectomy if indicated, generally followed by radiotherapy [30-34 63].
When the metastatic node is located at level IV or supraclavicular region, an excisional biopsy of the node is recommended. The pathologists should make every effort to identify the possible source in order to guide further diagnostic and therapeutic evaluation. In the case of a possible thyroid origin total thyroidectomy and Neck dissection (II-VI) should be performed. When the source of the primary cannot be detected the tumour is considerated as disseminate (M1) and chemotherapy is suggested.

Follow-up

Follow-up examinations are scheduled on an individual basis determined by the risk of recurrence, to survey for the appearance of the primary tumour, development of second primary tumours, to deal with morbidity from treatment and with comorbidity not directly related to the cancer itself.
During radiation therapy periodic examinations by the head and neck surgeon may be necessary in patients experiencing difficulty with nutritional intake, airway or pain control.
After all treatment is completed periodic examinations by the radiation oncologist and a dentist in patients that received radiation therapy are recommended. Thyroid function tests should be monitored if the patient received radiation to the lower neck since up to 30% of patients may develop subclinical or overt radiation-induced hypothyroidism [63 87].
Oncological checks depend on histology:
SCC, UCNT, adenocarcinoma
Clinical and fibrescopic check every two months in the first year, every four moths for second an third year, then every six months.
PET once a year.
Additional exams at the discretion of the physician.
Lymphoma and thyroid carcinoma
Based on specific protocols.
Neck metastases from other sites (e.g., breast, prostate, colon): a follow-up according to the specific protocols, associated to clinical and fibrescopic ENT evaluation.

Prognostic factors and patterns of failure

Several endpoints, including rates of overall survival, disease-free survival, distant metastases, loco-regional control, neck control and primary occurrence, have been used to evaluate the outcome of patients with cervical SCC metastases from unknown primary. Numerous clinical and physical factors associated with these endpoints have been reported. However, the impact of particular therapeutic strategies is difficult to assess retrospectively. Selection bias is unavoidable; for example ipsilateral irradiation is typically administered for advanced disease or poor performance status patients, whereas surgery is performed in early stages.

Squamous Cell Carcinoma

The majority of information available in the literature is referred to SCC.

The nodal status is considered the most important prognostic factor. In fact, the prognosis seems comparable to that observed in patients with overt primary and similar nodal stage [29]. For patients treated with neck dissection, other prognostic factors include the number of lymph nodes, grading and extracapsular extension [46].

Over the last 30 years, probably due to better pretreatment evaluation and more effective therapy, neck control and primary occurrence have improved in head and neck CUP patients [70]. The question of whether these effects have been translated into improved survival is debatable [27 70].

The pattern of failure depends on the treatment applied. According to some authors, in early stages neck dissection alone and radiotherapy alone are equivalent and provide satisfactory nodal control [26 27 29 78]. After extensive radiotherapy, the predominant patterns of relapse include neck recurrence and distant metastases [24 28 29 88]. The latter are observed in up to 33% of patients [6 70 79 89-91] and usually occur shortly after completion of treatment (median 0.9 years) [38 79], independently of the histotype.

The rate of emergence of the primary tumours varies greatly in particular series from 0% to 66% [6 26 28 29 35 46 72 89-91]. The highest rate was observed following exclusive surgery: the emergence rate of the primary tumour is about 25%, the median nodal recurrence rate, about 34%, and the 5-year overall survival rate, 66% [29 46 72 94 95]. The estimated actuarial risk of emergence of head and neck primary after extensive irradiation reaches 20% at 10 years [7 26-28 36 38 39 89 90 92 96 97]. The effectiveness of radiotherapy is illustrated by the fact that the risk of emergence of a primary lesion after extensive irradiation is similar to the occurrence of second tumour in a patient with overt head and neck cancer [24 29 38 46].

The median time to the occurrence of subsequent primary is about 21 months [6 38], and the most common sites are the oral cavity, oro- and nasopharynx, supraglottis, and lung [29 38].

Several Authors observed poor prognosis after a subsequent detection of the primary lesions in the case of cervical lymph node metastases from SCC: median survival of 15 months and, 5-year survival of 20% after the detection of the primary [19 35 92]. Other Authors attributed poor outcome to nodal relapse, but not to primary occurrence [20]. In some series, tumours arising later than 5 years after primary treatment were classified as second primaries [35], whereas in others, they were considered to be the site of origin [38].

The predominant site of relapse after radiotherapy includes neck, followed by distant metastases [24 28 29 46 88]. The crude risk of either nodal recurrence or distant metastases is at least twofold higher than the risk of developing a mucosal primary [46]. The benefit from extensive radiotherapy to the mucosa and bilateral neck should be weighed against acute and late morbidity (xerostomia, dysphagia, etc.) and the difficulties in re-irradiation in the case of subsequent primary emergence. Several retrospective studies show that ipsilateral neck radiotherapy is correlated with a primary occurrence rate similar to that observed after extensive radiotherapy [18 74 93 98]. For these reasons, many Authors perform an ipsilateral radiotherapy to the involved neck side [23 24 29 35 74 92-94 98-100].

Surgery (planned neck dissection) performed after radiotherapy showed persistence of nodal disease in up to 44% of patients [23 35 38 40]. Such a sequence was associated with poorer survival and with higher postoperative morbidity as compared to surgery followed by radiotherapy [35 38]. These outcomes may, however, be related to selection bias, as radiotherapy is typically attempted in patients with advanced, inoperable neck disease [35].

Amichetti et al. [80] applied local microwave hyperthermia and radiotherapy (median 70 Gy to bilateral neck and potentially primary sites) in a group of 15 patients with locally advanced squamous cell neck carcinoma from unknown primary. Overall response rate was 87%, and actuarial 5-year local control and overall survival rates were 65% and 29%, respectively. Both acute and late toxicities were moderate, however longer follow-up and larger patient groups are needed to evaluate the role of this approach.

Patients presenting with poor performance status, very extensive nodal involvement, distant metastases or bilateral low neck involvement are usually approached with palliative irradiation [36 41 101]. Palliative radiotherapy, independently of the radiotherapy regimen, is associated with an objective response rate of 65%, the symptomatic response rate of 57% at one year, and 25% one-year survival; these results are similar to those obtained with palliative chemotherapy, which would likely be more toxic and more expensive [41].

Undifferentiated and Poorly differentiated carcinomas

Results are similar to those of overt undifferentiated nasopharyngeal carcinomas.

Adenocarcinoma

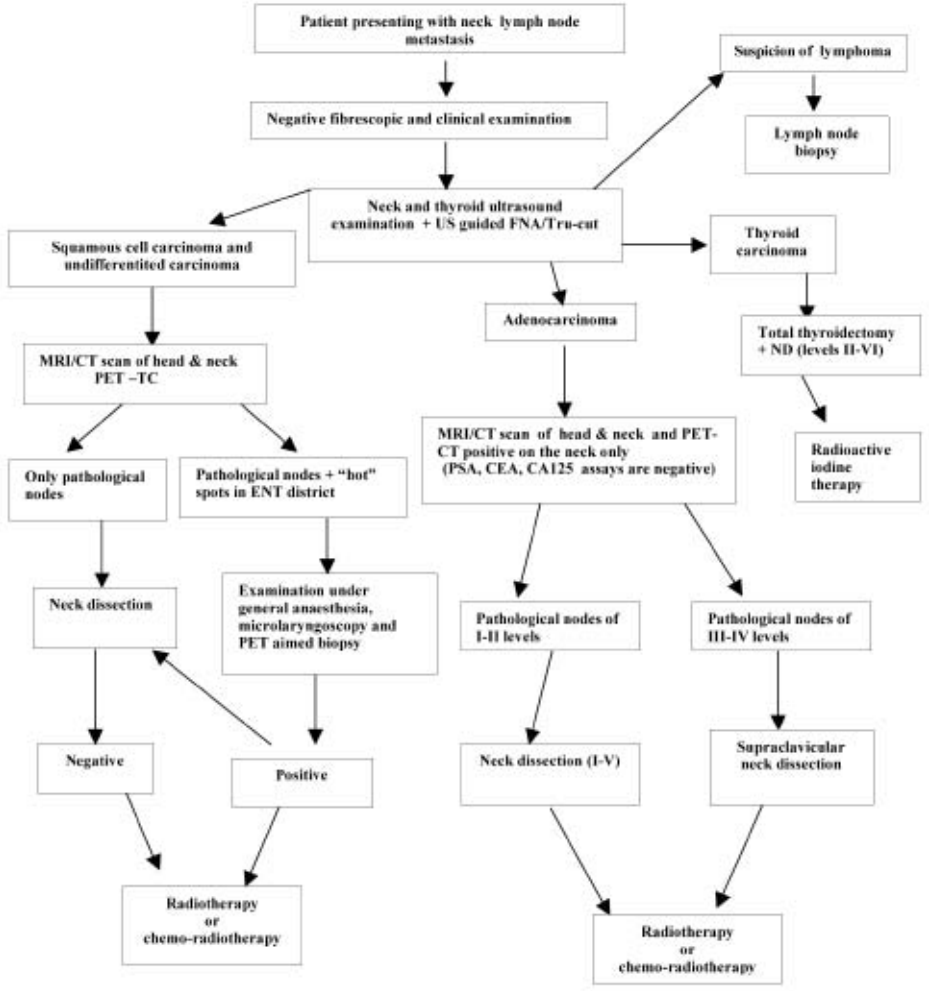
Prognosis of adenocarcinomas from unknown origin is poor, especially when level IV is involved: due to their rarity results are generally reported considering all metastatic sites [88 102].

Conclusions and future directions

Despite many studies addressing cervical metastases from unknown primary, the optimal diagnostic and therapeutic approach has not yet been established. The role of new investigational methods, such as PET, SPECT or laser-induced fluorescence, and the relevance of molecular assays still await critical evaluation. The optimal extent of surgery and radiotherapy has to be defined, both in terms of its efficacy and impact on patient quality of life. The value of other therapeutic modalities (such as chemotherapy, hyperthermia) should be further investigated.

Recently, the first randomized study on head and neck SCC CUP patients has been launched by the Intergroup including the European Organization for Research on Treatment of Cancer (EORTC), Radiation Therapy Oncology Group (RTOG) and other cooperative groups from Australia, Canada, Denmark and Germany (study 24001-22005). After surgery (radical neck dissection, modified or extended radical neck dissection, or selective neck dissection), patients are

Table II. Suggested diagnostic and therapeutic flow chart.



randomized either to selective radiotherapy (ipsilateral neck node area) or to extensive irradiation (naso-, oro-, hypopharyngeal and laryngeal mucosa and neck node areas on both sides of the neck). Patients with single level IV, Vb or I lymph node are excluded. The inclusion of pN1 patients depends on institutional policy. Systematic ipsilateral tonsillectomy is mandatory. The primary endpoint is disease-free survival, and the secondary endpoints include control of the neck, incidence of subsequent primary in the head and neck region, overall survival, acute and late toxicity, and quality of life. The results will be available several years only in time, but they should offer the answers to many questions regarding the management of head and neck CUP patients.

At the moment we are confident that the flow chart reported in Table II represents a useful diagnostic and therapeutic schedule.

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