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8. Multidisciplinary approach for the treatment of neuroendocrine tumors

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Multidisciplinary approach

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Introduction

Neuroendocrine tumors (NETs) are a fairly uncommon group of highly heterogeneous diseases with regard to their biological behaviour and clinical course. Despite the improved understanding and recognition of these tumors, they remain "orphan" diseases and much is still to be done to improve their outcome. In order to optimize patient care and improve survival, NET patients must be treated with a multidisciplinary team-approach in centers with a specialist interest.

Neuroendocrine tumors (NETs) are derived from different cells of the diffuse neuroendocrine system and can originate from any location in the body. NETs of bronchopulmonary and gastrointestinal origin were traditionally referred to as carcinoid tumors, but in the past decades there has been the increased recognition that this terminology does not account for the extreme heterogeneity and complexity of these tumors with regard to their biological behaviour and clinical course. In effect, today we have good reason to abandon the traditional carcinoid terminology (which however will not be completely left, especially with regard to pulmonary tumors) and to talk about endocrine or neuroendocrine tumors and divide them according to their site of origin. Specifically, this has been prompted by the increasing awareness that when we talk about carcinoids, we might talk about completely different diseases. A very good example is the difference between the carcinoids arising in the foregut, the midgut and the hindgut. In the foregut there are three types of stomach carcinoids, in the midgut we know that ileal tumors can produce the carcinoid syndromes with all specific related problems, like heart disease, flushing and diarrhea, generally occurring in the presence of metastases to the liver, whereas in the hindgut rectal carcinoids hardly produce any carcinoid syndrome and are more famous or infamous because of the local symptoms. We also know that some NETs (the so-called functioning tumors) can produce several biologically active hormones or peptides and in these tumors morbility and mortality are the results of hormonal or hormone-related symptoms, but can also be the consequence of problems caused by tumor expansion. On the contrary, more than half of NETs (the so-called non-functioning tumors) either produce no hormones or biologically inactive hormones, and remain symptomatically silent until a large tumor volume leads to non-specific symptoms such as jaundice, intestinal obstruction, abdominal pain etc. In these tumors morbidity and mortality mainly result from tumor mass or distant metastases. Because of the extreme heterogeneity and variability of these tumors, the management of NET patients poses many clinical challenges and requires a multidisciplinary approach based on the close cooperation of a variety of medical, imaging and surgical specialities. Centres of expertise for the diagnosis and management of NETs offer the patients evaluation from dedicated combined clinical teams including internists, endocrinologists, oncologists, pathologists, radiologists, nuclear medicine physicians, clinical geneticists, gastroenterologists, gastrointestinal/pancreatic/thoracic surgeons, transplant surgeons and also dedicated nurse practitioners.

The role of centers of expertise in the improved management of NETs

Although neuroendocrine tumors (NETs) have been considered as fairly rare diseases, their incidence and prevalence has increased substantially over the last few decades, which may be partly due to the improved understanding and recognition of these tumors, but maybe also to an actual rise in the number of cases. However, disappointingly this increased incidence has not been matched by an improvement in outcome, as demonstrated by data from the US Surveillance Epidemiology and End Results (SEER) database which reported no substantial change in 5-year survival for the period 1973-2002[1].

In the last years, the establishment of centers of expertise for neuroendocrine tumors with dedicated combined clinical teams for the management of NET patients have significantly improved survival compared with standard of care offered in non specialist facilities. Available evidence clearly indicate that patients are far better cared in centres of expertise, like the Uppsala Centre of Excellence for Endocrine Tumors of which

Prof Kjell Öberg is Chairman, compared to general centers (Figure 1).

NET multidisciplinary team involves a variety of specialists: internists, endocrinologists, oncologists, pathologists, radiologists, nuclear medicine physicians, clinical geneticists, gastroenterologists, gastrointestinal/pancreatic/thoracic surgeons, transplant surgeons and also dedicated nurse practitioners. Some centers have also a so-called tumor board, ie. a dedicated work group where all the specialities are represented and management strategies are discussed. In some countries, patient support groups too are increasingly assuming a central role. Multidisciplinary team decides on diagnosis and treatment depending on pathology, biology, epidemiology and research. All team members play a specific role in the multi-step diagnostic work-up and all of them contribute to different extents to the decisional process leading to a "tailor-made" therapy based on patients' specific disease and health status. Furthermore, by talking to each other team members can decide on future directions of research not only at a local level, but also at a national or international level.

Multidisciplinary team approach: some practical examples

The diagnosis of gastroenteropancreatic NETs involves a multi-faceted approach requiring careful and detailed pathological, gastroenterological, radiological and nuclear medicine work-up. We know that pathologists have played a relevant role in the diagnosis and understanding of NETs. They have provided significant tools such as WHO classification and ENETS TNM classification and grading system[2-4]. What's more important, several works have demonstrated that this grading system works, showing the huge difference between stage I and II tumors from stage III and IV tumors[5,6]. Thanks to this highly valuable tools, pathologists can provide very important information with regard to the future therapy of patients, because the stage III and IV patients really need different therapeutic approaches compared to the stage I and II patients.

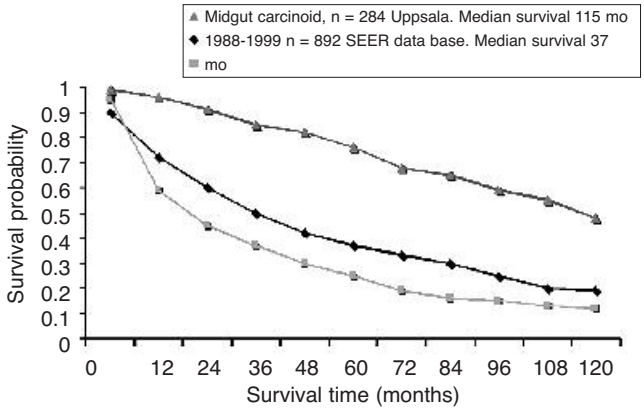

Figure 1 - Survival times in NET patients managed in a center of expertise compared with non specialist centers. Data from the Uppsala Centre of Excellence for Endocrine Tumors and from the SEER database. Published with kind permission of Professor K. Öberg.

Also assessment of the location and extent of the tumor is crucial for management. Commonly used imaging modalities for the study of NETs include conventional radiology and nuclear imaging. Imaging strategies are aimed at identifying disseminated disease (eg, computed tomography [CT] for the staging of the disease and somatostatin-receptor scintigraphy [SRS] for the determination of the somatostatin receptor status); they are necessary for the preoperative work-up of local tumor extent, to prove the source of symptoms and/or biochemical problems (eg, enteroclysis, CT/magnetic resonance imaging [MRI] enteroclysis, capsule endoscopy, SRS) and, again, to follow-up patients and to exclude recurrent disease (eg, CT, ultrasonography, MRI, SRS). No technique is 100% sensitive, and often multiple imaging modalities must be used to detect small, biochemically diagnosed tumors. At present, SRS is one of the most sensitive technique for the identification of metastases. ^{111}In-pentetreotide scintigraphy is a very excellent technique for staging and for determining dissemination of tumors, either thymic carcinoids with lymph nodes metastases or rectal carcinoids with lymph node metastases[7]. There is also the possibility of hybrid fusion imaging like SPECT/CT hybrid imaging with ^{111}In-pentetreotide scintigraphy[8], but the future perspective are oriented toward PET techniques, which provide superior imaging quality and higher resolution[9].

An example of the multidisciplinary team approach and of the "cross-talk" between oncologists, nuclear medicine physicians, pathologists, radiologists and pancreatic surgeons is provided by the case of a 59 year-old male with metastatic nonfunctioning pancreatic neuroendocrine tumor which was considered inoperable by the pancreatic surgeon. This patient complained of pain in the belly and couldn't eat a lot because his stomach was completely compressed by a massive liver that was expanding into the pelvic area and was occupying most of his abdomen. In 2004 it was decided to treat this patient with chemoembolization. As demonstrated by CT scans, the first cycle of chemoembolization led a decrease in liver size and also a slight decrease in tumor, followed by a further decrease in live size after the second cycle. The patient was then was treated with 4 cycles of peptide radioreceptor therapy (PRRT) with ^{111}Lu-otcreotate, which allowed to achieve tumor reduction as well as a general improvement in the patient's general conditions (Figure 2). The progressive decrease in tumor size was accompanied by a progressive reduction in CgA levels, which is an excellent marker of re-

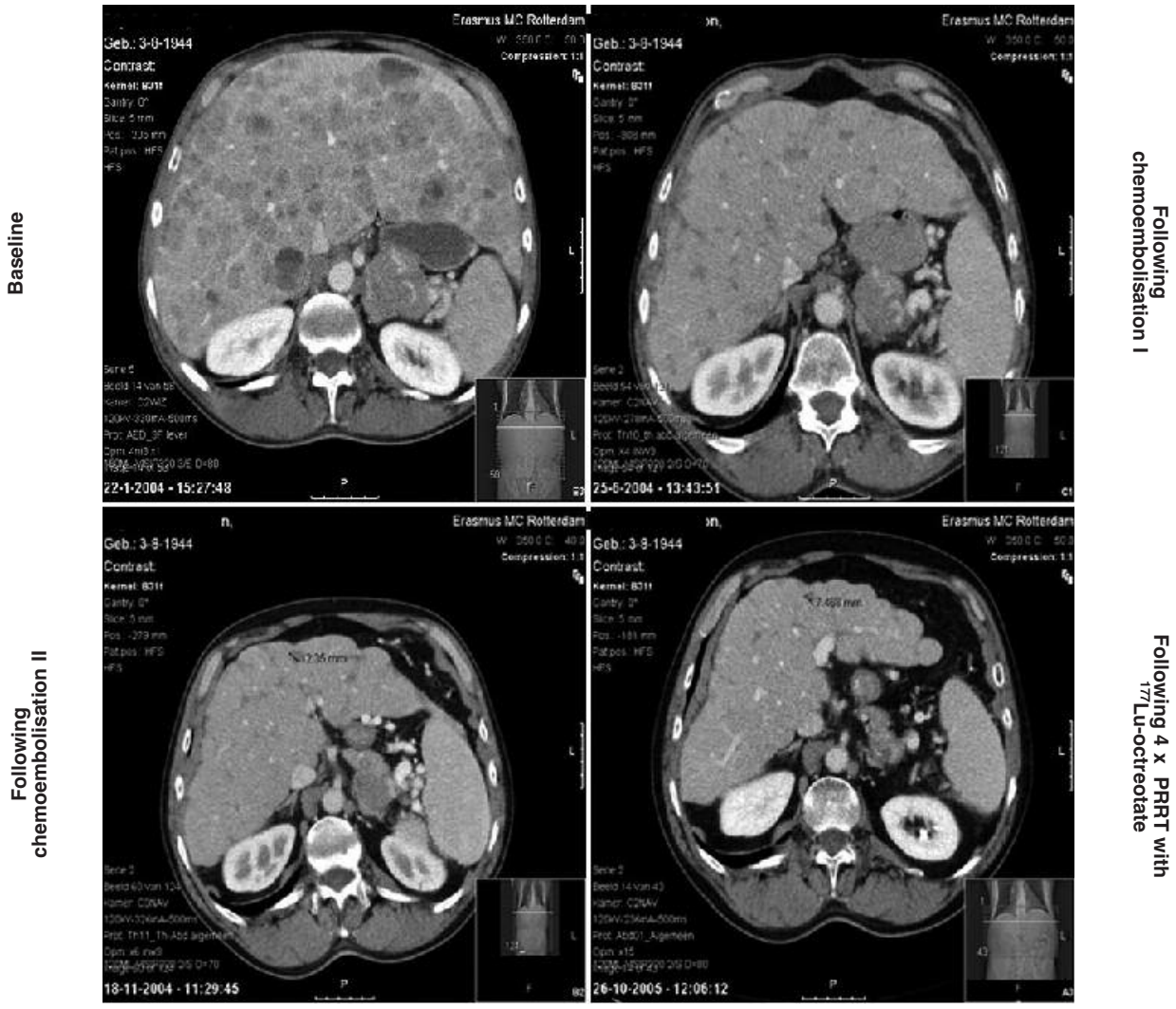

Figure 2 - CT images of a metastatic nonfunctioning pancreatic neuroendocrine tumor in a 59 year-old male patient at baseline, following the first and the second cycle of chemoembolization and following 4 cycle of peptide radioreceptor therapy (PRRT) with ^{111}Lu-otcreotate.

sponse to treatment (Figure 3). After downstaging using PRRT with ^{111}Lu-otcreotate, another patient with an initially large and inoperable pancreatic endocrine tumor could be successfully operated by the pancreatic surgeon.

Future requirements for improvement of NET outcome

Neuroendocrine tumors are characterized by extreme heterogeneity and complexity with regard to their biological behaviour and clinical course. Over the last decades, their incidence and prevalence have increased but survival of patients has not changed substantially, suggesting that there is still much to do to improve treatment strategies and NET outcomes (Table 1). Advances can be made also with

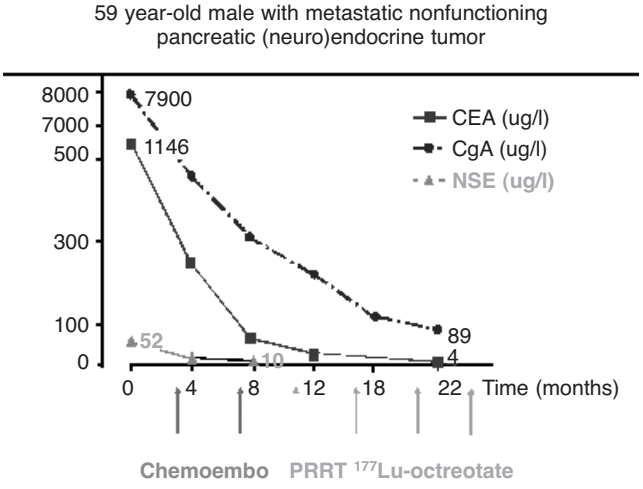

Figure 3 - Progressive reduction in CgA levels from baseline due to achievement of tumor reduction.

Table 1 - Requirements for an improvement in NET outcome[1]

- Refinement of universal classification and grading system
- Elucidation of cell biology
- Development of cell lines and animal models
- Acquisition of genetic information
- Identification of serum markers for early diagnosis
- Definition of tissue markers to identify tumor origin
- Development of molecular pathological profiling to define prognosis
- Precise identification of topographic information (before and during surgery)
- Identification of molecular therapeutic targets
- Development of improved (adjuvant) treatment for residual disease
- Establishment of centres of excellence and multidisciplinary speciality NET clinical teams
- Construction of central clinical and tissue database resources
- Government focus on clinical and research funding for an orphan disease

the development of centers of excellence that could treat patients with a multidisciplinary team approach, coordinate and join together in multicenter studies, enable international interactions between professionals and between professionals and patients, maintain clinical tumor databases and promote education.

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Surgical approach to the treatment of liver metastases from neuroendocrine tumors: hepatic resection and liver transplantation

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Introduction

In patients affected with neuroendocrine tumors (NETs) in the advanced stages, hepatic metastases are almost invariably the main factor associated with clinical worsening and the only independent factor affecting long-term survival. Despite the introduction of new therapeutic agents, surgical therapy remains the most efficient approach to liver metastases from NETs, especially those originating in the gastrointestinal tract. Liver R0-resection is an effective treatment and offers better survival than palliative treatment alone, but it is associated with high recurrence rate; liver transplantation can achieve the best available survival in patients with liver metastases from NETs of gut origin when proper selection criteria are applied.

Liver metastases develop in 40 to 93% of patients with neuroendocrine tumors (NETs) of the gastrointestinal tract[1] and are often present at the time of diagnosis. In patients affected with NETs in the advanced stages, massive liver involvement leading to hepatomegaly, discomfort and poor quality of life is almost invariably the main cause of clinical worsening and the only independent factor affecting long-term survival[2]. However, metastases from NETs follow frequently an indolent course compared with hepatic metastases from non-endocrine gastrointestinal or pancreatic malignancies, and can remain confined to the liver for prolonged periods, so that patients often can live many years even without treatment. Starting from the premise that it is

very difficult to conduct adequate clinical trial due to the rarity of these tumors[3], previous studies on limited series indicate that patients with untreated liver metastases from NETs have a median survival time of about 3 years and a dismal prognosis within 5 years from diagnosis, with survival rates of 21% in syndromic patients and of 11-40% in non syndromic patients at 5 years[2-4]. Despite the indolent course of these tumors, a timely intervention may be able to impact on the natural history of the disease. Although new therapeutic options have become available, surgery remains the most efficient and successful approach for the treatment of neuroendocrine metastases to the liver, offering the longest-lasting benefits in term of survival and symptoms control in comparison with other available treatment.

Recent results on resection of hepatic metastases from neuroendocrine tumors

Surgery is considered to be the most rationale approach for NET patients with metastases confined to the liver. However, curative resection of liver metastases (i.e., R0 resection, clear margins and absence of microscopic residual disease) is feasible only in 10-25% of patients, since in the great majority of cases residual tumor is always left behind as for a 5-year recurrence rate of about 80%[1]. For these reasons, resection is mainly regarded as a cytoreductive procedure ("debulking") with palliative intents for patients with large tumor bulk causing severe symptoms or a clinically relevant syndrome. The rationale underlying the choice of such a demanding procedure is that in these patients the removal of more than 90% of the tumor bulk can achieve a significant symptomatic relief which cannot be obtained with other non-surgical approaches[1].

Prospective studies comparing surgical resection of hepatic metastases from NETs with non-surgical approaches are lacking and available evidence is based mostly on single-institution experiences on limited series selected with widely different criteria. A review of literature data relative to the last four decades indicate that hepatic resection for liver metastases from NETs is associated with highly heterogeneous benefits, with OS rates ranging from 47% to 89% and DFS rates constantly well below 40% at 5 years[5-20]. The largest published series from the Mayo Clinic has been collected from 1977 to 1998[15]. In this series of 170 patients, overall survival after partial hepatectomy was 61% and 35% at 5 and 10 years, respectively, and median survival was 81 months. Recurrence-rate was very high, but a significant difference was observed between patients who underwent complete resection *versus* those who underwent incomplete resection (76% *vs* 91% at 5 years; median time to recurrence, 30 *vs* 16 months, respectively; $P = 0.0004$). Hepatic resection for neuroendocrine metastases, confirmed to be safe and achieved symptoms control in 96% of patients with consequent reduction of pharmacological therapy. The second very large series was collected at the Memorial Sloan-Kettering Cancer Center (MSKCC) from 1992 to 1998[18]: 85 patients were allocated either to medical therapy (n = 18), hepatic artery embolization (HAE, n = 33) or surgery (n = 34) based on a multidisciplinary case-by-case discussion. Data showed that surgical resection improved survival with respect to other options since the 1- and 3-year survivals for patients treated with medical therapy were 76% and 39%, respectively with no patients surviving at 5 years. Conversely, the 1-, 3-, and 5-year survival rates for patients treated by HAE and surgical resection were 94%, 83%, and 51% *vs* 94%, 83%, and 76%, respectively. Earlier resection of the primary tumor, curative intent of liver resection and surgical treatment proposed as first option were associated with prolonged survival, being a >75% liver involvement by tumor the only independent factor predictive of poor surgical outcome. In the attempt to predict surgical outcomes a scoring system was also developed taking into consideration the functional or non-functional status of the primary tumor (0 = functional, 1 = non-functional), the presence of extrahepatic disease (0 = no extrahepatic disease, 1 = extrahepatic disease), site of liver involvement (0 = unilobar, 2 = bilobar) and percent of liver involvement (0 = <75% involvement, 1 = >75% involvement). When applied retrospectively, this scoring system predicted both survival and resectability. A score of 0 was associated with a 5-year survival of 100%, and a score of 4 predicted a 0% 2-year survival. Interestingly, all patients in whom a complete, curative resection was achieved had scores ≤2 and showed significantly better survivals compared to patients with more advanced disease.

The role of surgical resection with curative or palliative intents in the treatment of hepatic metastases from neuroendocrine tumors has been recently confirmed by the ENETS Consensus Guidelines for the management of patients with metastatic NETs of the digestive tract[21]. According to the ENETS consensus statements, "Surgical resection remains the gold standard in the treatment of liver metastases, achieving a survival rate of 60-80% at 5 years with low mortality (0-5%) and acceptable morbidity (close to 30%). […] Debulking resections can exceptionally be justified in palliative situations; however, removal of at least 90% of the tumor volume is necessary. If the primary tumor is still present, it should be removed at this time as well".

Liver transplantation for metastatic NETs: salvage versus curative approach

Hepatic metastases from NETs are currently regarded as one of the few, if not the unique, indication to liver tranplantation in the metastatic setting[1]. However, the ideal candidate for liver transplantation, in case of

metastatic NET, is still a matter of debate. The established strategy for the management of patients with metastastic NETs had taken into account the option of liver transplantation (LT) as a salvage therapy for patients with very advanced disease. However in recent years the availability of more accurate prognostic information based on tumor characteristics and clinical features has led to the reappraisal of liver transplantation as a potentially curative strategy for highly selected cases of metastatic cancer[1]. As for surgical resection of hepatic metastases from NETs, the relative rarity of these tumors accounts for the lack of evidence on the real effectiveness of LT since available data relies mainly upon anedoctal reports or small retrospective studies on limited series rather than on large prospective studies. The most relevant series originates from the European Liver Tranplant Registry (ELRT) collecting 159 patients achieving 52% survival at 5 years. Thus may reflect a poor patient selection and a large heterogeneity of the collected patients from 1970 to 2009 achieving a survival rate ranging from 36% to 80% and recurrence rates from 9% to 48% at 5 years[22-31]. From 1989 and 1994[30] a significant series of 31 patients affected with metastatic carcinoid tumors and islet cell carcinomas was collected in France: OS and DFS were 36% and 17% at 5 years, respectively. Interestingly, however, survival rates were significantly higher for carcinoid tumors, namely low-grade NETs according to the last WHO classification (OS of 69% at 5 years), an observation which led the authors to restrict indication for liver transplantation to selected patients with liver metastases from carcinoid tumors.

Ten years later, the same multicentric group updated their results on 85 patients[30] with a follow-up of 46 months and median survival was 56 months; again liver transplantation for metastatic neuroendocrine tumors confirmed to be associated with an OS rate of 47% and a DFS rate of 20% at 5 years. Some independent factors predictive of poor prognosis after LT were identified: in particular, the use of simultaneous LT and resection of primary tumors, the duodeno-pancreatic site of the primary tumor (corresponding to the majority of non-carcinoid histology) and the presence of clinical hepatomegaly as expressed as >120% of estimated standard liver volume, which is somehow a surrogate of liver involvement.

A different approach to management of hepatic metastases from NETs has been also proposed recently by Frilling *et al.*[31], who selected 119 patients for aggressive treatment based on the different localization types and presentation patterns of metastatic spread[10]. Specifically, the Authors identified three different patterns of liver metastases: single metastasis of any size (type I); isolated metastatic bulk accompanied by smaller deposits, with both liver lobes involved (type II); and disseminated metastatic spread, with both liver lobes involved or single lesion of varying size and virtually no normal liver parenchyma (type III). Treatment of hepatic metastases was allocated in relation to localization types. Resection with curative intent was feasible in all 23 patients with type I liver metastases but in none of the 96 patients with type II or III. On the other hand, transplantation was used only in a small number of highly selected patients with type II or III unresectable liver metastases. When survival was analyzed according to localization of hepatic metastatic spread, significant differences were observed between the three types of metastatic spread, with type I yielding 5- and 10-year overall survival rates of 100%, compared with 84% and 75% for type II and 51% and 29% for type III, respectively.

Therefore, the localization and biological features of liver metastases from NETs are predictive of outcome, and have been used to develop an algorithm based on recommendations for diagnosis and treatment of neuroendocrine liver metastases[31]. In this algorithm, liver replacement has been used mainly for very advanced cases (type III), even with simultaneous resection of extrahepatic disease. Interestingly, with regard to the WHO classification the present study demonstrated that type I mainly consists of well-differentiated neuroendocrine carcinoma with a lower malignant potential, whereas types II and III encompass more aggressive, well-differentiated and poorly differentiated neuroendocrine carcinomas. The differences between the three types are presumed to represent true differences in biological behaviour rather than a time bias.

The ideal candidate for liver transplantation: the Milan criteria

At the opposite side of the aforementioned experience of Frilling *et al.*, which considers liver transplantation as a salvage procedure for patients with very advanced disease, our Institute Milan group regards liver replacement as a therapy with high potential not only of prolonging survival, but also of pursuing a curative intent[1]. At the beginning of our experience, more than 15 years ago, we selected a set of clinico-pathological criteria which allowed us to allocate patients on the basis of disease presentation at the moment of referral and to define whether a curative (ie, liver transplantation or resection of liver metastases with resection of primary tumor) or a palliative approach (ie, resection of primary tumor with non-surgical approach to liver metastases or medical therapies) could be pursued. Notably, these parameters take into consideration survival as the main end point, but also the exact life gain offered to patients by each strategy, compared with alternative options, disease-free survival for curative approaches and progression-free survival for palliative approaches.

The application of these parameters has led to the identification of the Milan criteria for indication to liver transplantation, which apply a strictly selective process

to transplant candidacy and enables to propose liver replacement only to patients most likely to be cured[32].

To date, 184 patients with NETs metastatic to the liver and no extra-hepatic spread has been referred to our department and allocated to treatment according to the Milan criteria. Of these patients, 23% (n = 42) received only medical therapy, 35% (n = 64) underwent resection of primary tumor, 25.6% (n = 47) underwent liver surgery in concomitance with primary resection, and 16.4% (n = 30) underwent liver transplantation. The mean age of patients who received only medical therapy was significantly higher compared with patients undergoing transplantation (55.8 ± 13.0 *vs* 40.1 ± 11.5 years). All patients undergoing radical interventions (liver transplant with or without resection of primary) had a confirmed diagnosis of low grade disease and all had a MIB-1 <20. It's worth noting that, since pancreatic primaries are most difficult to treat surgically and taking into account the curative intents and intended radicality of hepatic transplant, the pancreas was the primary tumor site only in 31.9% and 16.7% of patients undergoing radical resection and liver transplant, respectively, compared to 76.2% of patients who received medical therapy. CgA levels were significantly higher in patients treated with medical therapy compared to transplanted patients. None of the patients undergoing liver replacement presented with extra-hepatic spread. Tumor burden was similar across goups. Liver transplantation strategy and liver surgery plus primary resection strategy were associated with a overall survival approaching 96% and 88% at 5 years, respectively, compared with OS rates of about 64% and 38% reported for the resection of primary tumor only and medical therapy, respectively. Liver transplantation was also associated with a recurrence-free survival of about 80% at 5 years, which is significantly higher compared to the 34% rate reported for a non-transplant strategy. Although preliminarly, these data strongly suggest that liver transplantation is a feasible and potentially curative approach for selected cases of hepatic metastases from NETs with clear survival benefit in terms of freedom of recurrence.

Conclusions

Available clinical evidence confirms the effectiveness of the surgical approach to liver metastases from NETs with particular reference to primary tumors originating in the gastrointestinal tract. Liver R0-resection is an effective treatment and offers better survival than palliative treatment alone, despite high recurrence rate (up to 70-80% at 5 years). Debulking resections can be applied with palliative intents to pursue a significant clinical improvement otherwise not achievable with alternative non surgical-approaches, but require the removal of at least 90% of the tumor volume.

The role of liver transplantation as a salvage or curative approach is still debated. Our experience shows that liver transplantation can achieve the best available survival in patients with liver metastases from NETs of gut origin when proper selection criteria are applied. Timing of transplantation during natural history of disease should be discussed after an accurate evaluation of different achievable advantages. Benefit of transplantation is undetermined in the earliest stages of the disease, when too many variables do not allow an accurate prognostic evaluation, while is highest for tumors controlled by therapy and at an intermediate stage of liver involvement. Prospective multicentric studies are warranted to validate proposed criteria and to determine the role of biological parameters in different treatment strategies.

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The choice of surgery in thoracic neuroendocrine tumors

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Introduction

In the carcinoid tumors of the bronchopulmonary tract, surgical resection is still the primary goal. However, much controversy exists as to the most appropriate extension of resection or the opportunity to perform systematic lymphadenectomy to reduce the risk of recurrence. In particular, currently open surgical questions include the type of resection to be adopted, ie., whether it is to be conservative of the "parenchyma-saving" resection type, or whether it is to be extensive involving major pulmonary resection, and whether it is useful to perform lymphadenectomy routinely or only in those cases where N+ is present at clinical and/or surgical staging.

The surgical spectrum of neuroendocrine tumors of the bronchopulmonary tract

Thoracic neuroendocrine tumors account for 1-2% of all lung neoplasms. They comprise a heterogeneous group of neoplasms which differ for histologic characteristics and clinical behaviour and represent a wide spectrum of disease: at one end there are well-differentiated typical carcinoid (TC) tumors and at the other end there are poorly differentiated small cell carcinomas (SCCs). Intermediate degrees of differentiation and behaviour define the other neoplasms in this spectrum, ie. atypical carcinoid (AC) tumors, mixed large-small cell neuroendocrine carcinomas (LSNECs) and large cell neuroendocrine carcinomas (LCNECs)[1].

Specifically, the typical carcinoid is a relatively benign tumour whose clinical behaviour is typically non-invasive and involves lymph nodes in less than 10% of cases, whereas such involvement is till 50 per cent in atypical

carcinoids, which grow a little faster and are somewhat more likely to spread to other organs. ACs are less common that TCs, which tend to be centrally located, whereas ACs are most frequently observed in peripheral locations. Carcinoids typically presents with symptoms including hemoptysis, wheezing, cough, and dyspnea, but sometimes patients may be asymptomatic[1,2]. Endocrine manifestations in pulmonary carcinoids are rare, but can include the carcinoid syndrome, Cushing's syndrome, hypercalcemia, and acromegaly[1]. In general, patients with TC and AC tumors are on average 10 years younger than routinely encountered patients with more common lung epithelial carcinomas[2,3], have better respiratory performances and show a favourable prognosis, with survival rates ranging from 53% to 96%.

With regard to the therapeutic approach of the carcinoid tumors of the lung, surgical resection is still the primary goal[4]. SCCs, LSNECs and LCNECs, in contrast, are much more aggressive and are infrequently amenable to surgical resection because of the presence of lymph node involvement and/or distant metastases at diagnosis in the majority of cases.

Although the role of surgery as the principal therapeutic approach for TC and AC tumors is well-established, two questions are still controversial and deserve particular attention: the extension of resection and the necessity to perform hilar and mediastinal lymphadenectomy routinely or only in those cases where N+ is present at clinical and/or surgical staging.

Optimal surgical modalities for the carcinoid tumors of the lung

Surgical resections can be of conservative or extensive (radical) type. Conservative resections are aimed at parenchyma saving and include segmentectomies, wedge resections and bronchoplastic techniques, whereas extended resections involve major pulmonary removal and include pneumonectomies, lobectomies and bilobectomies (Figure 1).

In peripherally located TCs, segmentectomy represents the ideal type of surgical procedure, whereas wedge resection can be taken into consideration in patients with damaged pulmonary functions, even if its role in this indication is still debated. Segmentectomy or lobectomy are instead recommended in peripheral ACs. Carcinoid tumors in central locations are more challenging and can require a pneumonectomy with the risk of sacrificing large portion of the lung parenchyma. However, as a result of the significant advances in anaesthetic and surgical procedures, sleeve resection with bronchoplasty has recently gained wide acceptance as a much less invalidating alternative to pneumonectomy in patients with centrally located carcinoid lesions. Sleeve resection enables parenchymal preservation, does not alter outcome, allows to increase the bronchial safety margin and is not associated with a significant reduction in quality of life. Nevertheless, pneumonectomy is still necessary in patients presenting with a seriously compromised lung function induced by prolonged obstruction. Specifically, sleeve resection with total parenchymal preservation is recommended to

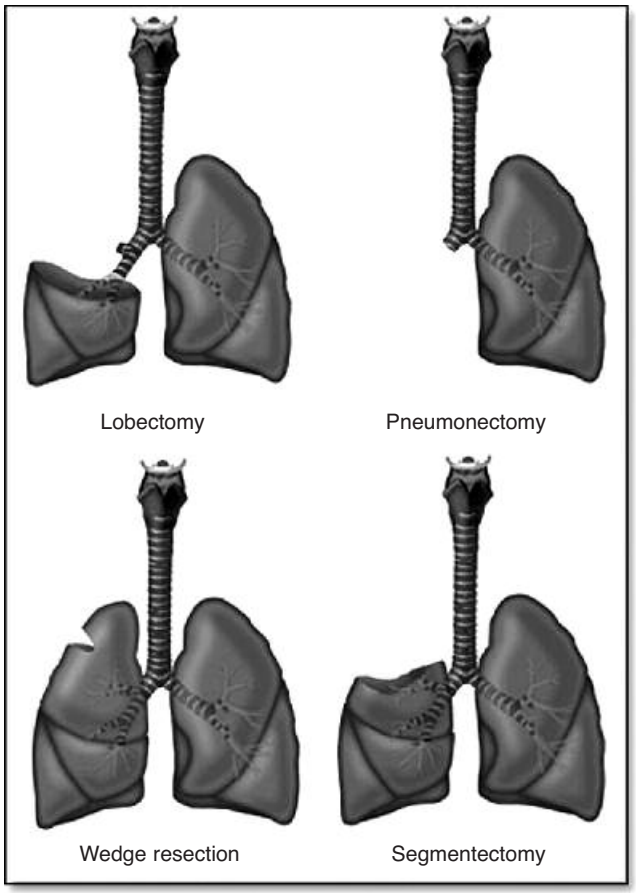

Figure 1 - Different types of surgical resections for the carcinoid tumors of the lung.

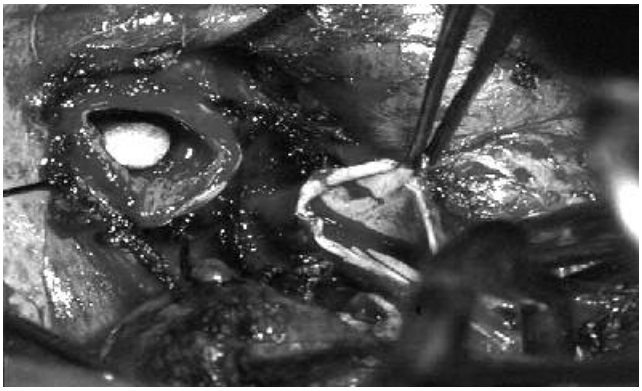

Figure 2 - Right upper sleeve lobectomy: bronchial margins after resection, before anastomosis.

treat lesions involving the tracheal carina, the principal or the intermediate bronchus. Lesions originating near the orifice of the lobar bronchus and showing evidence of extrabronchial infiltration are similarly amenable to sleeve lobectomy (Figure 2).

TC tumors have an excellent long-term prognosis, with disease-free survival (DFS) rates of 87-100% at 10 years. The prognosis of AC tumors is substantially poorer, as shown by the 10-year DFS rates of 31-83% reported in the literature. Regional lymph node metastases develop in 2-10% of TC tumors and in 15-50% of AC tumors and do not correlate with the primary volume and stage. Notably, both in TC and AC tumors lymph nodal spread significantly reduces survival[5,6]. So, for instance, in a study on patients (n = 55) with endobronchial carcinoids undergoing standard anatomic resection (lobectomy or pneumonectomy) with systematic hilar and mediastinal lymphadenectomy, it was found that histologic pattern (TC or AC) and nodal status (pN0 or pN1) were the only prognostic factors which significantly influenced disease-free survival (P = 0.002 and P = 0.05, respectively). In this study, disease-free survival rates of patients with nodal involvement (pN1+Nmi) were 83.3% at 5 years and 55.6% at 10 years, in comparison to 100% in patient without nodal involvement (P <0.0001)[6]. Detection of lymph node micrometastases by anti-cytokeratin and anti-chromogranin A monoclonal antibodies allowed a more accurate staging of endobronchial carcinoids. Owing to the rather high rate of lymph nodal spread and to its significant impact on survival, systematic hilar and mediastinal lymphadenectomy should be performed in any carcinoid patient[6].

With regard to the choice of surgical intervantion in this setting, it is worth noting that the diagnosis of lung carcinoid tumor is made by the surgeon in the great majority of cases, and that it is often difficult to ascertain the typical or atypical feature of a bronchial carcinoid during surgery. For this reason, we believe that both typical and atypical carcinoids should be managed preferentially by an anatomic resection (lobectomy or segmentectomy) associated with systematic lymph node dissection. Bronchoscopic resection alone appears suboptimal because it does not allow lymph node staging and identification of multicentrico forms, being often not curative and lacking some of the prognostic information essential for therapeutic decisions.

Conclusions

Neuroendocrine tumors (NETs) of the bronchopulmonary system constitute a wide spectrum of disease ranging from the well differentiated typical carcinoid (TC) tumors to poorly differentiated small cell carcinoma (SCC). Despite the common denomination of neuroendocrine tumors, lung NETs are characterized by a totally different clinical behaviour, and this requires a precise surgical and clinical strategy for each different histological subtype. In particular, the high-grade SCCs and large cell neuroendocrine carcinomas (LCNECs) display typically an aggressive behaviour and are often widely disseminated at the time of diagnosis, which make them infrequently amenable to surgery. Radical surgery is instead indicated for the less aggressive TCs and atypical carcinoids (ACs), although there is still much controversy as to the most appropriate extension of resection or the opportunity to perform systematic lymphadenectomy to reduce the risk of recurrence. Based on the data published in literature and on our experience, we believe that segmentectomy represents the ideal type of surgical procedure in peripherally located TCs. Segmentectomy or lobectomy are instead recommended in peripheral ACs. With regard to centrally located carcinoid tumors, sleeve resection with bronchoplasty has gained wide acceptance as a much less invalidating alternative to pneumonectomy. Notably, in carcinoid tumors of the lung prognosis is more related to nodal status than to histologic subtype. For this reason, systematic hilar and mediastinal lymphadenectomy is always necessary in both TCs and ACs.

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GEP NETs *versus* thoracic NETs: what is similar and what is different?

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Introduction

Neuroendocrine tumors (NETs) of the bronchopulmonary system encompass a wide range of pathologic entities that display distinct biologic behaviors. In the 1970s, bronchopulmonary NETs were classified into three histologically defined categories: the low-grade, well-differentiated typical carcinoids (TCs), which metastasize infrequently and have an excellent prognosis; the intermediate-grade, well-differentiated atypical carcinoids (ACs), which were first reported in 1972 by Arrigoni *et al.*[1]; and the highly malignant, poorly differentiated small cell lung carcinomas (SCCs), which metastasize frequently and have a dismal prognosis.

In 1999, the classification of lung NETs was further revisited following the recognition by Travis *et al.* of large cell neuroendocrine carcinomas (LCNECs) as another highly malignant, poorly differentiated category of pulmonary NETs, distinct from both typical and atypical carcinoids and SCCs as well[2]. Considerably, in the lung setting the carcinoids and the carcinomas represent two different worlds and, as such, they must be kept well separated.

Carcinoids of the lung represent almost exclusively the domain of surgery. The diagnosis of well-differentiated thoracic NETs is done by the surgeon in the great majority of cases, and preoperative diagnosis is a rather rare occurrence. If there is the clinical suspicion of a clinical syndrome, for instance the carcinoid syndrome, and a lesion in the thorax, imaging studies with PET-CT or somatostatin receptor scintigraphy can be performed, with the evaluation of laboratory markers such as CgA or 5-HIAA. The treatment of choice remains surgery.

This paper provides a general overview of the differences and similarities between gastroenteropancreatic neuroendocrine tumors and thoracic neuroendocrine tumors with particular reference to epidemiology, prognosis, molecular markers and therapy.

Epidemiology

Epidemiology of lung NETs varies greatly between well-differentiated and poorly differentiated forms. The well differentiated forms, TCs and ACs, are quite rare tumors and account for a very small proportion of lung cancers. The TCs show a prevalence of 1-2% and are more frequent than ACs, the prevalence of which is estimated to be 0.1-0.2%. Among the poorly differentiated forms, SCCs represent one of the most common histological sybtypes and account for 20% of lung cancers, whereas LCNEC is a much less common NET subtype and accounts for 3% of lung cancer[3].

In the Western world, carcinoid tumors of the bronchopulmonary system are one of the most frequent type of neoplasms of neuroendocrine origin. As demonstrated by data from the US Surveillance, Epidemiology, and End Results (SEER) database relative to the period 1973-2005, pulmonary NETs account for more that 25% of all carcinoid tumors, with the remaining 75% of cases represented by carcinoids from the gastroenteropancreatic tract[4]. The estimated incidence of lung NETs is of 1-2/100,000 inhabitants per year, compared to about 2.5-5 cases per 100,000 reported for gastroenteropancreatic neuroendocrine tumors (GEP NETs)[4-6]. In a epidemiological analysis on 2391 patients diagnosed with carcinoid disease from 1989 to 1997, the main primary site of carcinoid tumors was the appendix (27%) followed by the lung (22%)[5]. Notably, in the largest series reported by Modlin *et al.* from 1973 to 2005, a sharp increase in incidence of lung carcinoids has emerged, but it is still unclear whether such an observation is related to advances in diagnostic techniques or is due to a real increase[4,7].

With regard to aetiology, a strict correlation between cancer and cigarette smoking has been reported for both SCCs and LCNECs, with about 95% of patients affected by these tumors showing a history of tobacco abuse[8]. The same correlation has not been observed for carcinoids. The average age at diagnosis of patients with bronchopulmonary carcinoids is generally a decade younger compared with patients with SCCs and LCNECs (50-60 years *vs* 60-70 years, respectively). A higher female prevalence has been referred in carcinoids, whereas SCCs and LCNECs seem to be more prevalent among men. Moreover, in both TCs and ACs, but not in SCCs and LCNECs, neuroendocrine cell hyperplasia with or without associated tumorlets is a relatively common finding. Tumorlets are significantly more frequent than carcinoid tumors and may be multifocal and bilateral. They are very often associated with inflammatory processes like bronchiectasis and interstitial fibrosis, and the correct histological diagnosis requires an accurate serial dissection of the pulmonary parenchyma. The real significance of these lesions is still not completely understood and it is debated whether they represent an 'early' stage of carcinoid[8]. In addition, similarly to GEP NETS carcinoids that can develop synchronous and metachronous secondary tumors, which conversely are generally absent in the LCNECs. This may be related also to the fact that patients with LCNECs have shorter survivals and generally they do not live enough to develop secondary malignancies. Finally, combined tumors can be found in about 10% of the poor-differentiated forms of lung NETs, and are detected in increasing percentages in lung carcinoids[8].

Prognosis

If we put into correlation the WHO classification of lung NETs with the WHO classification of gastroenteropancreatic neuroendocrine tumors (GEP NETs), which distinguishes between the two major categories of well-differ-

entiated, NETs (tumor/carcinoid and malignant carcinoma) and poorly differentiated, NETs (typically small cell endocrine carcinomas), we find that the typical carcinoid correlates completely with the well-differentiated GEP tumors, and the atypical carcinoid correlates with the well-differentiated malignant carcinoma in the GEP system as well. However, getting into the high-grade, poorly differentiated categories, in the thoracic setting there is the LCNEC that can hardly be found in the GEP system, even if recent data indicate a rather high rate of LCNECs of the hindgut especially in Japan[9]. Thus, while the poorly differentiated large cell carcinomas are rather common in the lung, they can rarely be found in the GEP NET system, where the poorly differentiated small cells carcinomas are typically much more frequent than the large cell carcinomas. Reasons of this discrepancy between the lung and the GEP systems are still unclear, and probably will be addressed in future studies in the field of cellular and molecular biology.

According to the grading system proposed in the 1999 WHO classification, the main distinctive criteria for each type of lung NETs are as follows: carcinoid morphology, mitotic rate <2 per 10 high-power fields (HPF), absence of necrosis for TCs; carcinoid morphology, mitotic rate ≥2 and <10 or coagulative necrosis, evidence of necrotic areas for ACs; neuroendocrine morphology, positive immunohistochemical staining, cytological features of an NSCLC, mitotic rate ≥10, large necrotic zones for LCNEC; small size, scant cytoplasm nuclei, finely granular nuclear chromatin, absent of faint nucleoli, mitotic rate ≥10, frequent and large areas of necrosis for SCC[10]. Interestingly, the mitotic rate in the lung system is generally low when compared to the related tumor categories in the GEP system (<2 for low-grade, well-differentiated tumors, 2-20 for intermediate-grade, well-differentiated carcinomas and >20 for the high-grade, poorly differentiated carcinomas). The 1999 WHO grading system has clearly demonstrated its value as the strongest predictor of survival in lung NETs patients, allowing to detect significantly prognostic differences between TCs and ACs as well as between ACs and LCNECs plus SCCs. Several reports on the prognosis of lung NETs have reported. Travis et reported 5-year survival rates of 87%, 56%, 27%, and 9% for TCs, ACs, LCNECs and SCCs respectively[11], whereas Garcia-Yuste *et al.* reported corresponding rates of 96%, 72%, 21%, and 14%, respectively[12]. Neither report described a significant difference in survival between LCNECs and SCCs. As for LCNEC, the reported 5-year survival rates have ranged from 13% to 47%. In a more recent study by Asamura *et al.* The 5-year survival rates for patients with TCs, ACs, LCNECs, and SCCs were 96.2%, 77.8%, 40.3%, and 35.7%, respectively. The histologic type as NET significantly affected the prognosis of the patients (P = 0.0001). The prognosis of AC was significantly better than the prognosis of both LCNEC and SCC (P= 0.0406), which means that intermediate-grade malignancy (AC) could be differentiated from high-grade malignancy (LCNEC and SCC). The survival curves of LCNEC and SCC were superimposed, and there was no difference in survival (P = .9147), which means that the high-grade neuroendocrine histology uniformly indicated poor prognosis regardless of its histologic subtype[13]. With regard to survival, it is worth noting as once again the TCs correlate completely with the well-differentiated tumors in the GEP system in that they show an excellent 5-year survival, and the same correlation exists between the lung ACs and the neuroendocrine carcinomas of the GEP system, which are associated with comparable, significantly lower survival rates at 5 years. Survival become significantly even worse in both the SCCs and the LCNECs and correlate well with the poor survival observed in poorly differentiated carcinomas of the GEP system.

In lung carcinoids, however, besides histology another important variable pertaining to tumor stage largely influences long term survival, namely the nodal status and the tumor size. With regard to the nodal status, survival is excellent in absence of lymph node metastases, but significantly worsens when nodal involvement is present. Several works in the literature have assessed the role of lymph node involvement as prognostic indicator according to the WHO TNM staging system, and have reported survival rates at 5 years of 97-100% and 83-100% in presence of N0 involvement, 75-100% and 54-79% in presence of N1 involvement, and 50% and 0-22% in presence of N2 involvement for TCs and ACs, respectively[14-18]. Interestingly, a main aspect differentiating the thoracic setting from the GEP NET system is that prognosis of lung carcinoids varies according to the different anatomic locations of the lymph nodes involved. Patients presenting with limited hilar or peribronchial involvement but usually show a better prognosis compared to those with mediastinal involvement or distant lymph node involvement, for instance in the supraclavicular or contralateral region. It must be underlined that in the GEP NETs such detailed nodal staging is lacking. This is due of course to a pure anatomical reason differing with regards to lymphatic drainage.

Further data from literature indicated also that a higher mitotic rate (>5, P <0.001) and a tumor size of 3.5 cm or greater (P = 0.017) were negative independent predictors of prognosis in patients with ACs[19]. As far as tumor size is concerned, another experience from the Mayo Clinic on pulmonary ACs has shown that a primary lesions of 3 cm or less was associated with a very good survival after resection, whereas primary lesions larger than 3 cm as well as nodal involvement were predictors of a poor prognosis[20].

Molecular markers

Evidence on molecular markers in lung NETs is still scarce. As a consequence, the use of such markers in the clinical practice has not yet been established and awaits

validation from further studies. A study by Grandberg *et al.* on 43 patients with typical bronchial carcinoids have suggested that analysis of CD44, Bcl-2 and p53 might provide information about the biology of the typical bronchial carcinoid tumor thus contributing to the prognostic evaluation of patients. Specifically, positive staining for p53m, and also for Bcl-2, has resulted strongly correlated to distant metastases and decreased survival, whereas the lack of CD44 expression was strongly associated to a decreased risk for distant metastases and death[21]. With regard to the p53, it is worth noting that this marker has a prognostic value in the poorly differentiated neuroendocrine carcinomas of the GEP system, where it is quite often positive, while it seems to play no role in the well-differentiated GEP NETs. The potential prognostic relevance of p53 has been confirmed by Przygodzki *et al.*, who found that AC tumors show subcategories of immunohistochemical reactivity to p53, and that the immunohistochemical staining intensity of p53 has a predictive value on patient survival. In particular, the patients' subgroup of ACs with p53 focal or patchy immunohistochemical staining had a significantly worse outcome compared to the AC negative subgroup, with significantly decreased time of survival and a higher probability of tumor recurrence. The authors concluded that the use of p53 immunostaining may be helpful to delineate AC cases at higher risk for aggressive behaviour[22].

As far as LCNEC is concerned, disruption of the Rb pathway most frequently by loss of Rb protein has been reported[23], while a significantly poor outcome has been observed in patients exhibiting allelic imbalance at chromosome regions 6q25 and 6p[24]. Finally, a Bcl2/Bax ratio >1, a marker of antiapoptotic status, has also emerged as a potential predictor of poor survival in LCNEC[25].

Medical therapy

Current data on medical therapy for thoracic NETs are still rather few and derive from very small series, but future perspectives appear to be promising. Of course, patients with a TC undergoing R0 resection do not need any medical treatment. On the other hand, in progressive patients adjuvant therapy must be must selected after an accurate evaluation which should take into account the extent, the grade and the stage of the disease.

The treatment of choice for patients with well differentiated, functioning lung NETs are somatostatin analogues, whereas chemotherapy is reserved for poorly differentiated and progressive tumors. As in GEP NETs, somatostatin analogs achieve a good control of symptoms and disease stabilization as well, but most probably have no significant effect on tumor growth.

Evidences from small series indicate also the beneficial effects of the combination of alfa-interferon (α-IFN) with octreotide. Interestingly, the use of this combination therapy in 27 patients with lung carcinoids resulted in 44% of symptomatic responses, 63% of biochemical responses and 41% of radiological responses[26]. As far as poorly differentiated lung carcinomas are concerned, combination chemotherapy with cisplatin and etoposide have a long and well-established use, and can achieve response rates ranging from 40 to 80%, even if prolongation of survival does not exceed 3-6 months [for review see 27]. However, new chemotherapeutic regimens deserve evaluation in this setting, such as CapOx (capcitabine/oxaliplatino) and FolFox (leucovorin/5-fluorouracil/oxaliplatin). Finally, the alkylating agent temozolomide has demonstrated antitumoral activity with acceptable toxicity. In a study on 36 patients with advanced NETs (including 13 bronchial carcinoids), treatment with temozolomide 200 mg/m^2 for 5 days every four weeks resulted in a overall objective radiological response rate of 14% and a biochemical response rate of 19%. Stabilization of disease was observed in 53% of patients[28].

Conclusions

The carcinoids and the carcinomas of the lung represent two different worlds and must be kept well separated. The staging and grading systems proposed in the existing WHO classification of lung NETs are the most powerful and valuable tools to predict the clinical behaviour of these tumors and the survival of patients, and must be kept into consideration in the choice of the therapeutic approach. Carcinoids of the lung represent almost exclusively the domain of surgery, whereas chemotherapy is reserved to LCNECs and SCCs. Adjuvant therapy is required for pN2 atypical carcinoids and LCNECs. Meaningful molecular markers are awaited in well-defined subgroups of patients.

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