Consensus of the French Endocrine Society

Malignant insulinoma: Recommendations for characterisation and treatment

Insulinome malin : caractérisation et traitement

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A PubMed search was performed, using the keywords: “insulinoma”, “neuroendocrine pancreatic tumors”, “islet cell carcinoma”, “malignant insulinoma”, and limited to reports on human adults and English-language publications (except for French-language guidelines), including case reports.

Due to its rarity, there is currently no dedicated guidelines for treatment strategy and follow-up specific to malignant insulinoma [1]. Management is generally assimilated to that for well-differentiated functional pancreatic endocrine tumors [2]. The hypoglycaemia-related morbidity and mortality of malignant insulinoma, however, requires strategic adaptation. The guidelines presented here are therefore based on published data relating to:

- symptomatic control of benign and malignant insulinoma;
- antitumoral control of malignant insulinoma;
- symptomatic and antitumoral control of functional and/or non-functional pancreatic neuroendocrine tumors (NETs).

The European and American treatment guidelines for pancreatic NETs have been taken into account [2,3]. A consensus of French experts was sought for each treatment proposal. The low level of evidence of the publications (level 4) precluded guidelines above grade C (expert opinion).

1. Definition, epidemiology

Insulinoma malignancy is confirmed by presence of extrapancreatic locoregional, lymph-node or remote extension. Insulinoma is malignant in 4–14% of cases [4–10].

Two other definitions, based on pathology results, are used in the current guidelines:
• insulinoma of uncertain prognosis (size greater than 2 cm or grade 2 based on the 2010 WHO classification, or vascular and/or perineural invasion or necrosis);
• benign insulinoma if none of the above.

Very few prognostic series dedicated to insulinoma have been published yet. Therefore it seems important to keep the characterisation as broad and precise as possible, awaiting data from large well-characterized cohort of patients with prolonged follow-up to refine diagnostic and prognostic factors. Parameters, listed above, were selected according to retrospective studies of pancreatic NETs or insulinomas [8,11–13].

2. Characterisation

2.1. Pathology

Insulinomas are categorised according to the 2010 WHO, 2007 ENETS and 2010 UICC-pTNM classifications of NETs. The vast majority present as well-differentiated tumors and poorly differentiated insulinoma seem not having been reported in the literature. Even so, given the prognostic importance of the differentiation status and a few reports of unusual aggressive clinical presentations of malignant insulinoma that mimics poorly differentiated carcinoma, the prognostic importance and therapeutic impact of such classification is to be underlined [14–16].

The ENETS and UICC-pTNM classifications require the pathologist to specify the size and number of resected nodes, how many of these are metastatic, extrapancreatic extension and degree of invasion.

Insulinoma is usually discovered as a localised tumor, with recovery demonstrated by the disappearance of hypoglycaemic symptoms in more than 90% of cases. In such setting lymph-node status is usually unknown.

The median size of malignant insulinoma at diagnosis ranges from 2.3 to 6.2 cm [4,8,17,18]. There is no absolute threshold of size corresponding to malignancy: in three reports, 40–80% of metastatic insulinomas measured less than 2 cm [5,7,17].

Certain criteria of the 2004 WHO classification no longer appear in the new 2010 WHO classification like necrosis and vascular or perineural invasion; we nevertheless consider them as noteworthy while prognostic series dedicated to insulinoma are lacking. The quality of resection (R status) and the number of tumors are also worth being recorded.

2.2. Anatomic location

Most (>99%) malignant insulinomas are pancreatic. There is no clear pattern of intrapancreatic location, although certain authors consider caudal locations to be the most frequent [5,7,17]. When there is no identifiable pancreatic primary lesion, an extrapancreatic location should be considered as an alternative to the presence of a small insulinoma [19].

2.3. Clinical presentation

Onset of malignant insulinoma is typically in the 5th or 6th decade of life. No sex predominance has been demonstrated. Malignant insulinoma is by definition functional, characterised by clinical hypoglycaemic manifestations together with low plasma glucose and inadequate insulin secretion, which are relieved by intake of sugar. The frequency and severity of symptoms and their impact on quality of life, the level of anxiety or depression of the patient and his or her close relations should be assessed. During hospitalisation, the psychological impact of the patient’s symptomatology on the health-care team should also be taken into account. Clinical manifestations of malignant insulinoma are similar to those of benign forms [10], but may be more severe and prolonged due to the greater production of insulin and proinsulin by the metastatic tumoral mass. Conversely, malignant insulinoma may be first diagnosed as a non-functioning pancreatic NET becoming secondarily functioning. The severity of hypoglycaemia thus varies from patient to patient and there is no strict relationship with the tumor burden.

Time to diagnosis from first onset of neuroglycopenic or adrenergic symptoms is also variable, from 1 month to 17 years [17,20]. Synchronous metastasis appears to be the most frequent presentation. Rarely, malignancy is diagnosed at the time of recurrence: according to Hirshberg, this is the case of 2% of insulinomas as a whole. The frequency of metachronous liver metastasis in malignant insulinoma as reported by two teams was respectively 8% and 11% [7,17], with an interval of 3 or 9 years [8,17].

Although this has not been definitely demonstrated in insulinomas, relapse could be more frequent in insulinoma classified as pancreatic tumor of uncertain prognosis according to the 2004 WHO classification, for which prolonged surveillance is therefore advisable [21].

2.4. Biological markers

The diagnosis of organic hypoglycaemia is made on the basis of clinical and biological criteria. Biological markers, however, have no demonstrated role in prognosis or follow-up. Exploration is conducted in the same way whether a benign or malignant tumor is suspected. The criteria and thresholds for biological diagnosis of inappropriate hyposecretion of insulin (≥3 mU/l) or of proinsulin (≥5 pmol/l) with concurrent hypoglycaemia (≤0.45 g/l) are similar [22]. However, insulinemia and C-peptide levels 2 to 3-fold higher in malignant forms, and 72h-fast test more rapidly proved positive were reported malignant insulinoma [4,17].

Once symptoms have been brought under control, the usefulness of regular surveillance of glycaemia is debatable and should be reserved for periods of assessment or severe forms, being possibly anxiogenic for the patients and relatives.

Chromogranin A, which is elevated in 50% of cases, should be measured, as in any pancreatic NET [17]. Other hormonal assays are to be considered on a case-to-case basis, according to clinical presentation [20].
2.5. Genetics

More than 97% of malignant insulinomas are sporadic and rarely reveal any genetic predisposition syndrome. A few cases associated with MEN-1 and 1 case associated with type-1 neurofibromatosis have been reported [23]. Systematic genetic analysis is thus not recommended. Relevant records on personal or familial history compatible with a genetic predisposition syndrome, clinical examination and calcium assessment are recommended. In MEN-1, there is no phenotype-genotype correlation indicative of malignant insulinoma; there has, however, been a report of three male members of an Iranian family bearing a (c199,200del2) mutation who developed insulinoma that was in two cases malignant [24]. In addition, malignant insulinoma may be multiple, with no demonstrable genetic syndrome [17].

2.6. Morphologic and functional imaging

Morphologic and functional imaging is performed to specify the staging and guide the indication of metabolic radiotherapy. Dissemination is primarily intra-abdominal and locoregional, affecting the first lymph-node relays, adjacent tissue (adipose tissue and vessels) and peripancreatic organs (spleen, stomach, biliary tract, liver, etc.) [25]. Liver metastasis is also frequent [20]. The classic subsequent extension of pancreatic NETs is to the mediastinal nodes, neck and bone or, more rarely, the pulmonary parenchyma [26]. A few cases of locally advanced forms, known as “giant insulinoma”, have been reported [27].

Pretreatment assessment should include abdominopelvic CT with early liver arterial phase, possibly associated to hepatic MRI to determine pancreatic and hepatic involvement. Endoscopic ultrasound plays an important role in locating the insulinoma, determining the anatomic relation to the pancreatic ducts and vessels and exploring for multifocal involvement and lymph-node metastasis. If liver invasion is diffuse, thoracic CT or spinal MRI should also be performed.

Functional imaging by somatostatin receptor scintigraphy (OctreoScan®) is performed to localize the primary and look for metastases. It is on average positive in 50% of cases [28–31]. Uptake level should be qualified in view of possible metabolic radiotherapy. Other markers for medical functional imaging (FDG, GLP1 or Gallium-labelled somatostatin analogues) have been shown valuable [28,32–34].

In case of relapse, imaging assessment should look for multifocal pancreatic lesions, lymph-node extension, liver metastases, which may be microscopic, best diagnosed by liver MRI or celioscopy.

3. Prognosis

Pathologic classification in terms of well-differentiated tumor or poorly-differentiated carcinoma is the first step of the prognostic classification. In the vast majority of cases, malignant insulinomas are well-differentiated, and presence of liver metastasis is the major determinant of prognosis [17,35]. The prognostic significance of lymph node metastasis is now well established for pancreatic NET as a whole. At the metastatic stage, initial assessment should specify tumor volume (notably for liver metastases), progression on two successive morphologic assessments, proliferation index and co-morbidity. Uncontrolled hypoglycaemia, liver tumor burden exceeding 30% of the liver volume, morphologic progression and Ki67 index greater than 10–20% are factors of poor prognosis.

In an epidemiological study, Lepage identified 81 cases of malignant insulinoma in 30 European registries between 1985 and 1994, with 5-year survival of 55.6% [36]. Survival as reported in single-centre studies, was poorer: 16% 5-year survival in the Sao Paulo (Brazil) series with patients at advanced stage (89% rate of liver metastasis) [4]; 29% 10-year survival in the Mayo Clinic series of 13 cases over a period of 60 years [6]; median survival of 19 months in relapsed patients in Danforth’s report of 17 personal cases seen between 1957 and 1982 at the National Institute of Health, Bethesda, analysed together with 45 cases from the literature (all stage IV) [18].

Causes of death have not been reported in all studies. When analysed, however, a wide range of causes were described including suicide, central catheter infection, pulmonary embolism, myocardial infarction associated with diabetes and excess weight, as well as tumor progression. Such causes of death highlight the need for multidisciplinary management, vigilance with respect to vascular and septic risk factors and psychological follow-up. Respective mortality associated with hypoglycaemia or tumor progression is, at the present time, unknown.

4. Treatment

Treatment objectives are 2-fold: tumoral and hormonal secretion controls. In malignant insulinoma, the risk of hormone-related deaths or sequelae makes symptom control of major importance. At metastatic stage, all treatment options are palliative. In the absence of randomised comparative studies, prescription depends upon exact determination of the risk/benefit ratio of each treatment modality. Expected efficacy with respect to hypoglycaemia is also taken into account but rarely reported. Individualising predictive factors and response substitution markers is still in its preliminary steps.

4.1. Hormonal secretion control

Hormonal secretion control should be initiated within the first consultation. Given the gravity of hypoglycaemia, the treatment objective can only be complete symptomatic response. In case of suspicion of residual hypoglycaemia, short hospital admissions are advisable, to check that glycaemia is strictly normal. Hence, in the absence of data on long-term control of hypoglycaemia under purely symptomatic medical treatment, tumor burden debulking should be systematically discussed.

Symptomatic treatment comprises:

- general measures:
  - diet: fractionated feeding rich in slow sugars, advice on use of slow and fast sugars to restore glycaemia in case of malaise,
enteral nocturnal feeding if necessary, at home or in repeated short-term hospital admission,
● central venous catheterisation (double in case of regular glucose perfusion), to be envisaged according to severity of hypoglycaemia, with strict respect of asepsis,
● identification or choice of a person of trust among the patient’s family or friends, to be taught to recognise and react to signs of hypoglycaemia,
● provision of telephone contact number where the care-team can be reached at any time,
● initiation of early psychological support for patient and family,
● driving to be avoided and possibly forbidden;
● medical antisecretion treatment:
  o diazoxide 50–1500 mg/day is the usual first-line treatment for symptomatic control. It controls insulin secretion by opening potassium channels [37]. It is fast-acting but effective in only 50% of cases of insulinoma, and efficacy in malignant insulinoma is unknown. However, symptom control over periods of several years and even unexpected development of diabetes has been reported. Side-effects occur in 50% of cases: palpitation, nausea, anorexia, hirsutism, or sodium and water retention, which may be improved by thiazide diuretics, which increase the effect of diazoxide [38,39]. Progressive dosage is recommended, beginning with low doses. When no efficacy is seen, diazoxide should be discontinued, as there is no evidence that combination of drugs improves the symptomatic control. Certain authors have suggested that somatostatin analogues may inhibit the hyperglycaemic effect of diazoxide,
  o somatostatin analogues constitute an alternative to diazoxide in second line, and are well-tolerated and fast-acting. Their action is based on SST2 and SST5 receptor expression controlling insulin secretion in the tumor. The dose is 150–2000 µg per day by subcutaneous injection, which may be followed up by intramuscular injection of a slow-release form (long-acting Sandostatin LP 20–30 mg or Lanreotide 60–120 mg every 4 weeks) once efficacy has been demonstrated [25,40]. An initial subcutaneous dose delivered in hospital is advised, given reports of paradoxical hypoglycaemia [38,41–43]. Although there are several reports of long-term benefit in malignant insulinoma, the quality of the long-term symptomatic control remains unclear [17,44,45]. When no efficacy is seen, somatostatin analogues should be discontinued, as there is no evidence of benefit in association with diazoxide. The role of pasireotide in this indication is not known and paradoxical hypoglycaemia could be even more frequent given the higher inhibition of SST3 and SST5 receptors,
  o there have recently been several reports of the interest of everolimus in malignant insulinoma with intractable hypoglycaemia [33,46–49]. These initial reports found that everolimus gave remission of hypoglycaemia, allowing glucose perfusion to be discontinued in several cases, or termination of all other treatment for a period of months. The effect can be rapid, within days [33]. A recent report from the French Groupe d’Étude des Tumeurs Endocrines confirmed this benefit since a control of hypoglycemia was found in 11 out of 12 patients with no recurrence [49]. Everolimus is an inhibitor of the PI3K/AKT/mTOR pathway, which is abnormally activated in NETs. Recently published results from several phase-II and one phase-III trial demonstrated an antitumoral effect of everolimus in pancreatic NET. Hyperglycaemia and also hypertriglyceridaemia are side-effects of everolimus exploited for insulinoma treatment. Inhibition by everolimus of the AMP/Jun/Fos pathway may lower insulin secretion, but can also cause insulin resistance [50]. A fall in beta-cell count under everolimus is another possible mechanism of hyperglycaemia [50]. Main side-effects are aphthae, fatigue, diarrhoea, hypophosphoraemia and interstitial pneumopathy, requiring tailored follow-up [51]. Given its toxicity, everolimus is to be placed in third line for symptom control after failure and/or intolerance to diazoxide and somatostatin analogues,
  o other treatments: oral corticosteroids (prednisone, dexamethasone) have been used on an occasional basis, with ambivalent results, after failure of the above treatments [52]. Their rapid action gives them a role in symptomatic control; side-effects (including immunosuppression and heightened risk of sepsis), however, require alternatives to be found. It should be recalled also that chronic steroid therapy is a contraindication to everolimus therapy in the RADIANT trials suggesting that such combination should be avoided [53]. Use of beta-blockers, phenytoin (Dihydan®) and also calcium inhibitors and interferon in malignant insulinoma was reported in the past [54–56], although without proof of real and sufficient efficacy.

4.2. Antitumoral treatment

Antitumoral treatment combines general and/or locoregional therapy. The advent of metabolic radiation therapy and targeted molecular therapy has increased the range of treatment options. If symptomatic control is incomplete, in case of large tumor burden, tumor progression or exceptional poorly differentiated forms, antitumoral treatment should be performed urgently. The benefit of the various antitumor options when addressing hypoglycaemia control has been poorly described in the literature.

4.2.1. Locoregional antitumor treatment

4.2.1.1. Surgery. In malignant insulinoma, surgery is indicated in well-differentiated locally advanced or metastatic forms; it requires an experienced surgeon and anaesthesiologist [57,58]. Surgery is the only potentially curative treatment in malignant insulinoma diagnosed at a locally advanced stage. It may be indicated as first-line treatment or, after objective response to an initial antitumoral treatment. Surgery should attempt a complete resection of all macroscopic lesions. Mesenteric artery invasion is a contraindication to surgery. At the metastatic stage [59–61], palliative liver surgery is classically of interest when more than 90–95% of the macroscopic tumor mass can be removed and/or symptom control is deficient. In addition, the
tumor burden should be slowly progressive and the Ki67 prefer-
ably below 10% [62,63]. In certain cases, given the potential
ground of hypoglycaemia, less ambitious surgery is undertaken,
resecting 60–70% of the liver metastases. The benefit, however,
remains undetermined. Surgical mortality should not exceed 5% 
even at the metastatic stage. Five-year survival in most series 
of selected well-differentiated NET exceeds 70% but specific 
results in malignant insulinoma patients were not mentioned.
Relapse after surgery is 75% by 10 years, which highlights the 
fact that resection is never microscopically total, as was recently 
demonstrated [64]. Abdominal lymph-node, peritoneal and or 
ossous metastasis may also be considered for surgical resection 
on a case by case basis. Surgical strategies are thus widely used 
in malignant insulinoma [4,7,17]. Like in other well-differentiated 
NET, survival benefit is not known and the contribution to 
symptom control has been little described [5,8,20]. Given the 
impact of symptom control and the possibility of macroscopically 
complete resection, surgery should be system-
atically discussed as a first-line line antitumor option. American 
guidelines consider liver transplant in young patients without 
controlled secretion and with exclusive hepatic extension [3]. 
Five-year survivorship after transplantation in the absence of 
risk factors is 66% [62,63].

4.2.1.2. Hepatic chemoembolisation. Transarterial liver 
embolisation (TACE) is frequently used in metastatic malignant 
insulinoma, being easily accessible in practice and one of 
the few options which has been shown to produce a quick-
acting on secretion [4,30,46]. There are several reports 
of longstanding symptom control [30,65–67]. TACE is applied 
in well-differentiated NET that is inoperable, incompletely 
resected or evolutive [68,69]. In French, American and 
European guidelines, it is recommended as a second-line 
locoregional option after surgery [19,33,70]. Various tech-
niques are available, and the choice of the technique is presently 
governed by practical availability, feasibility based on tumor 
presentation and by contraindications. Published series for 
well-differentiated NET report tumoral response in 30–70% 
of cases, the best response being especially observed when 
involvement of the hepatic parenchyma is less than 30%, 
metastases are vascularised and/or the metastases treated are 
less than 3–5 cm in size [68]. Two treatment sessions are 
often performed, with subsequent sessions depending on the 
quality of symptomatic and tumoral response. When TACE 
needs to be repeated frequently, association to or, a systemic 
treatment may be considered. The associated morbidity and 
mortality is increase in case of large tumors and systemic 
treatment should be considered as an alternative in such 
cases.

4.2.1.3. Hepatic radiofrequency ablation or cryoablation. 
Hepatic radiofrequency ablation is currently used to treat small 
metastases of well-differentiated NET [71]. It was only recently 
introduced, and may be performed percutaneously or comple-
mentarily to liver surgery, destroying metastases inaccessible to 
surgery. French and European guidelines place the technique as 
a second-line locoregional option when surgery is not feasible 
[19,70]. Nevertheless, in the case of insulinoma, radiofrequency 
ablation, having low associated morbidity, may be an interest-
ing alternative to surgery for small tumors or patients with high 
surgical risk, or in case of uncertain short-term prognosis. There 
have been a few reports of symptomatic benefit in malignant 
insulinoma [17,20]. Metastasis size, ideally less than 3 cm, is 
the main predictive factor for response to radiofrequencies. The 
technique is also used to treat pulmonary nodules and, more 
recently, bone metastases. Mortality is low, at less than 1%. 
Alternatives such as microwave ablation are under assessment. 
Cryotherapy may be associated to liver surgery, to spare the 
parenchyma in case of multiple small lesions.

4.2.1.4. External radiation therapy. External radiation therapy 
is indicated for painful or unstable secondary bone lesions, cuta-
neous and cerebral metastatic locations [72]. The benefit in 
well-differentiated tumors has not been well studied: stabilisa-
tion is the most frequent short-term response. The role of external 
radiotherapy in controlling primary tumors, and pancreatic 
tumors in particular, at the metastatic stage has not been deter-
mined. The development of stereotactic surgery broadens the 
range of indications for external radiation therapy, positioning 
it as a new alternative to locoregional techniques as a whole in 
localised tumor.

4.2.2. Systemic treatments

Systemic treatments are discussed in patients who remain 
symptomatic despite the above-mentioned treatments or whose 
tumor is considered aggressive like patients with greater than 
20% tumor progression per year according to the RECIST crite-
ria, large tumor volume (≥ 30% liver invasion, bone metastasis), 
Ki67 index greater than 10% or with an exceptionally poorly dif-
ferentiated tumor type [13,73]. Systemic treatment should also 
be considered whenever locoregional treatments need to be 
frequently repeated (at less than 6 months’ interval). Pancreatic 
NETs are relatively chemo-sensitive and recent phase-III tri-
als with everolimus and sunitinib have demonstrated benefit in 
progression-free survival. The rarity of randomised studies and 
the lack of predictive factors for tumoral response make the 
best sequence uncertain. At all events, systemic treatment pre-
supposes rigorous assessment of the clinical and morphological 
targets, repeated at least every 3 months.

4.2.2.1. Poorly differentiated malignant insulinoma. This 
subgroup was recently renamed G3-neuroendocrine carcinoma in 
the recent 2010 WHO classification. It has not been definitely 
proved that malignant insulinoma can present as poorly differ-
entiated, although some reports of unusually aggressive forms 
raise the question [14–16]. It is therefore important to state that 
the reference chemotherapy for poorly differentiated neuroen-
docrine carcinoma is an association of etoposide and cisplatin 
[74–76].

4.2.2.2. Well-differentiated malignant insulinoma. This 
subgroup was renamed G1 or G2-NET in the recent 2010 WHO 
classification. Optimal treatment sequence remains to be deter-
mined. Chemotherapy and metabolic radiation therapy, however,
more frequently ensure objective response and should be considered as first-line systemic treatments whenever a reduction in tumor volume is sought.

4.2.2.2.1. Somatostatin analogues. The antitumoral action of somatostatin analogues has not been thoroughly assessed in malignant insulinoma, and precise guidelines for use cannot be laid down. Their symptomatic benefit, tolerance and simplicity, however, make them an attractive option, and it is noteworthy that tumor stabilisation was achieved in 18–57% of cases for a median 18 months in several reports that include primary pancreatic NET [77–84]. This was confirmed in a recent report from the German network concerning mainly grade-I ileal tumor of small metastatic volume, in which time to progression was increased by Sandostatin® LAR. Thus, long-acting somatostatin analogues are an option in small-volume, slowly progressive and/or low-grade malignant insulinoma. Again, absence of paradoxical hypoglycaemia should be first evaluated by subcutaneous injection.

4.2.2.2.2. Chemotherapy in well-differentiated pancreatic malignant insulinoma (G1-G2 NET). Chemotherapy plays an important role in well-differentiated pancreatic NETs in general and, by extension, in malignant insulinoma. Reports, however, have not specified symptomatic benefit in terms of hypoglycaemia control [4,5]. French and European guidelines recommend chemotherapy in first line for pancreatic tumor of poor prognosis [2,70]. European and American guidelines suggest everolimus as an alternative in case of malignant insulinomas [2,3].

For monotherapy, several older series reported antitumor efficacy for 5 fluouracil, doxorubicin, streptozotocin and dacarbazine [85–87]. More recently, antitumor efficacy was reported for temozolomide, with 8% or 34% objective response in two retrospective series of 12 and 53 patients, respectively [88,89]. In 1992, Moertel established the first reference chemotherapy regimen, demonstrating survival benefit with an association of adriamycin and streptozotocin compared to 5-fluouracil-streptozotocin or chlorozotocin [90,91]. This trial has not been replicated yet. The initially reported objective response rate of 69% has been brought down to 6–40%, without complete response, in more recent series [90,92–94]. In 5–10% of cases, surgery can be considered after a response has been obtained. Median response duration is 9–19 months. Alternative regimens are under development. Indeed, two studies suggested the interest of associating 5-fluouracil to oxaliplatin or gemcitabine to oxaliplatin, with 27% and 40% objective response in 11 and five patients, respectively. Finally, a recent phase-II trial reported 70% objective response with an association of capectabine-temodal as first-line treatment for well-differentiated pancreatic NETs [95]. Thus, at present, three chemotherapy regimens have shown signs of antitumor efficacy, but comparative studies are lacking. Their toxicity profiles and the individual comorbidities are thus the key elements in the therapeutic choice. The guidelines recommend the combination of streptozotocin to doxorubicin and 5-fluouracil in first line, since more data are available for these associations. Cardiologic and nephrologic surveillance is recommended.

4.2.2.2.3. Peptide receptor radionuclide therapy (PRRT). PRRT uses somatostatin analogues, labelled with radionucleides, which internalised within neuroendocrine cells after their binding to the somatostatin receptors. European guidelines recommend the use of octreotide or octreotide labelled with yttrium or lutetium [96]. Being poorly accessible, this treatment is recommended in all guidelines as a second-line option for aggressive forms. Nevertheless, metabolic radiation therapy is an alternative to chemotherapy, to be considered in case of elevated uptake at the somatostatin receptor scintigraphy. [90Y-DOTA\(^0\),Tyr\(^3\)] octreotide achieves some complete tumoral responses (2–5%) and a partial objective response rate varying from 7 to 22% for mean cumulative activity per patient of 5–13 GBq [97–104]. These studies also reported clinical improvement in 34–100% of cases [98,100,104,105]. The first, recently published, phase-II multicentre study in refractory carcinoma reported 4% objective response and a median progression-free survival of 16 months [106]; symptomatic control was achieved in 50% of cases for a median duration of 3 months. [177Lu-DOTA\(^0\),Tyr\(^3\)] octreotate seems to be the most interesting radiolabelled peptide in terms of receptor affinity and internalisation [107]: Kwekkeboom et al. reported 2% complete and 26% partial objective morphologic response in 131 patients treated with cumulative activity ranging from 22.2 to 29.6 GBq [108]. Predictive factors for response to treatment were strong uptake at the diagnostic scintigraphy and small liver metastasis volume. The same team demonstrated a positive impact on quality of life in a series of 50 patients, with improvement in fatigue, insomnia and pain scores [109]. The main side-effects were hemototoxicity, fatigue, and digestive disorder (nausea, vomiting, anorexia) [110]. Long-term severe impairment of renal function and myelodysplasia has been reported. Age exceeding 70 years, bone metastasis, history of chemotherapy and creatinine clearance less than 60 ml/min are factors for higher toxicity [111], in which case alternative treatment should be considered. Of note, rapid symptomatic response has been reported in several cases of patients with malignant insulinoma treated by metabolic radiation therapy [47,112,113].

4.2.2.2.4. mTOR pathway inhibitors. The first phase-II study demonstrated 7% objective response in 15 progressive pancreatic NET treated with temsirolimus [114]. Subsequently, 9% objective response and progression-free survival of 9.7 months were reported in a stratified phase-II study of everolimus in 115 patients with pancreatic NET [53]. Finally, two studies combining everolimus with octreotide reported respectively 27% and 4% objective response in 30 and 45 progressive or non-progressive pancreatic NETs, with progression-free survival of 16 months [53,115]. A recent randomised double-blind phase-III study of everolimus versus placebo in well-differentiated progressive pancreatic NET demonstrated a significant benefit in progression-free survival in the everolimus arm (11.4 months versus 4.6 months with placebo) [116]. Objective response was obtained in less than 5% in the everolimus arm, and no benefit in overall survival emerged. This treatment recently received European market authorisation for the treatment inoperable progressive well-differentiated pancreatic NET. Although recommended as second line for well-differentiated pancreatic
NET therapy in French and European guidelines, everolimus is recommended as an alternative first-line therapy in the specific case of malignant insulinoma. Indeed, the combinations of its hyperglycaemic and antitumoral effect make everolimus an ideal therapy especially in the case of tumors presenting with asymptomatic low tumor burden.

4.2.2.2.5. Antiangiogenic treatments. Objective response rates of 16%, 19% and 11% were successively reported in phase-II studies of sunitinib, pazopanib and sorafenib in pancreatic NET, with 70%, 81% and 61% 6-months progression-free survival, indicating antitumoral efficacy [117–119]. A recent randomised double-blind phase-III study of sunitinib versus placebo in well-differentiated progressive pancreatic NET showed significant clinical benefit in terms of progression-free survival in the sunitinib arm (11.4 months, versus 5.5 months with placebo) [120], with a 9% objective response rate. Initial claims of benefit in overall survival were not confirmed on later analysis. This treatment recently received French market authorisation for the treatment of inoperable progressive well-differentiated pancreatic NET. However, a risk of onset of severe hypoglycaemia has since been reported with sunitinib [121,122]. Therefore, the use of sunitinib in the setting of malignant insulinoma requires additional investigations before this agent can be considered as an option [122]. Studies of combinations of antiangiogenic agents and chemotherapy are presently underway [123,124].

4.2.2.2.6. Trials. Due to their uncertain behaviour, patients with malignant insulinomas are only rarely enrolled in trials. Specific trials should be envisaged.

5. Follow-up

In benign insulinoma, no surveillance is indicated. In insulinoma of uncertain prognosis, although the interest of surveillance is unproven, two assessments (clinical examination and abdominal MRI) are recommended every 6 months to 2 years for the first 10 years and then every 2 to 5 years all lifelong. This strategy should be reviewed as soon as a sufficient cohort of patients under prolonged follow-up is reached. Such follow-up has to be proposed also in case of incomplete R1 resection.

In malignant insulinoma, surveillance should be adapted in the light of symptom control and tumoral prognosis. Following resolution of hypoglycaemia, clinical and morphological assessments should be made at 3 months and repeated every 6 months in case of stability. The role of glycaemia monitoring is controversial.

The nutritional status, the psychological impact on patient and family, the strict rules of asepsia when dealing with central catheter should be assessed in parallel with symptomatic and tumoral control and monitoring of treatment tolerance.

Future studies should seek to determine the quality (efficacy, duration) of symptom control in parallel with assessment of tumor response.

6. French guidelines for the management of malignant insulinoma

The guidelines are as follows (Figs. 1 and 2):

- complete and lasting control of symptoms is the prime therapeutic objective;
- diazoxide or somatostatin analogues are the first-line treatment options for the control of hypoglycaemia;
- everolimus is recommended as a second or third-line in case of intolerance or progressive failure of control on diazoxide
or somatostatin analogues therapy, especially in case of low tumor burden;
- liver chemoembolisation can be an emergency treatment for severe hypoglycaemia resistant to medical management given its antisecretory action especially in case of poor prognostic outcome;
- surgery is indicated when macroscopically complete resection of primary and metastases is feasible with low risk (<3–5%) of morbidity or mortality. At least two morphological assessments should be made to check tumor slow progression. Other locoregional techniques as a whole are alternative treatments;
- other antitumoral options are to be considered loss when functional control is lost or in case of tumor of poor prognosis:
  - in operable stable or weakly progressive well-differentiated tumors with medically controlled symptomatology, macroscopic tumor reduction should be considered, using low-morbidity techniques,
  - in inoperable symptomatic tumor resistant to medical or locoregional treatments or in case of large liver tumor volume or progressive tumor, the medical options are metabolic radiation therapy, systemic chemotherapy and everolimus. Everolimus is indicated for persistent hypoglycaemia. Chemotherapy is to be considered in case of large tumor volume and/or rapidly progressive tumor. Metabolic radiation therapy depends on access to an equipped centre and on scintigraphic somatostatin receptor uptake. Metabolic radiation therapy is to be considered in case of large tumor volume and/or slowly progressive tumor.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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