Langenbeck's Archives of Surgery (2019) 404:31–37
https://doi.org/10.1007/s00423-018-1740-8

ORIGINAL ARTICLE

Main pancreatic duct dilation greater than 6 mm is associated with an increased risk of high-grade dysplasia and cancer in IPMN patients

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Received: 3 May 2018 / Accepted: 10 December 2018 / Published online: 5 January 2019

Abstract

Introduction IPMNs, considered precursor lesions of pancreatic adenocarcinoma (PDAC), might display histological alteration varying from low-grade dysplasia (LGD) to cancer. Nevertheless, the prevalence of PDAC is far below the prevalence of IPMN; therefore, not all of these precursor lesions finally progress to cancer. Preoperative features consistent with and finding at final histology of high-grade dysplasia (HGD) or cancer are currently lacking. The aim of this study is to correlate the presence of preoperative clinical features with the finding of advance lesions at final histology.

Methods This is retrospective cohort analysis of patients who underwent surgery for histologically confirmed IPMNs at Karolinska University Hospital, from 2008 to 2015.

Results MPD 6–9.9 mm and ≥ 10 mm were associated with an increased risk of HGD/cancer (respectively, OR 2.92, CI 1.38–6.20, $p = 0.005$ and OR 2.65, CI 1.12–6.25, $p = 0.02$). Preoperative high CA19.9 and jaundice were both associated with a higher risk of HGD/cancer at final histology (respectively, OR 4.15, CI 1.90–9.05, $p = 0.0003$ and OR 15.36, CI 1.94–121.22, $p = 0.009$). At sex- and age-adjusted multivariable logistic regression analysis, MPD between 6 and 9.9 mm (OR 2.64, CI 1.15–6.06, $p = 0.02$), jaundice (OR 12.43, CI 1.44–106.93, $p = 0.02$), and elevated CA19.9 (OR 3.71, CI 1.63–8.46, $p = 0.001$) remained associated with the occurrence of HGD/cancer.

Discussion The presence of MPD dilation ≥ 6 mm, jaundice, and elevated CA19.9 in IPMN patients are consistent with the finding for HGD/cancer at final histology, thus representing possible markers of advanced lesions suitable for earlier or preventive curative surgical treatment.

Zeeshan Ateeb and Roberto Valente contributed equally to this work.

Study highlights

What is current knowledge:

Pancreatic IPMNs are considered the precursor lesions of pancreas cancer but not all of them progress to cancer.

Preoperative clinical/radiological characteristics consistent with advanced lesions at final histology are currently lacking.

What is new here:

MPD ≥ 6mm, jaundice, and high CA19-9 are consistent with an increased risk of advanced histology in IPMN patients.

Those criteria might improve diagnostic accuracy and therefore increase the chances to achieve a curative treatment.

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Keywords Intraductal papillary mucinous neoplasms of the pancreas (IPMN) · Pancreas cancer prevention · Early diagnosis · Pancreas surgery · Pancreatic cystic tumors

Introduction

Pancreatic cancer (PDAC) is the fourth most common cause of cancer-related deaths in the Western world and is estimated it will to rise to the second most common cause by 2030 [1, 2]. In contrast with other tumor histotypes, PDAC's biologically aggressive behavior and the absence of effective medical therapies highlights the need for effective screeening programs for those at risk. PDAC's prognosis has remained virtually unchanged for the last 30 years in part because a method for screening for prevention and early treatment of pancreatic cancer and its precursor lesions has not been established. In the last decades, new data have shown that intraductal papillary mucinous neoplasms of the pancreas (IPMNs) can progress from adenomas to cancer [3, 4]. IPMNs can progress to pancreatic cancer, have a high prevalence in the general population, and are generally found incidentally on traditional cross-sectional imaging [5, 6]. However, the preoperative diagnostic accuracy of pancreatic cystic neoplasms is quite low even in third-level centra [7], and currently, there is no method is available to accurately predict the grade of dysplasia of an IPMN before surgery. This lack of diagnostic accuracy results in an increased risk of surgical mismangement, unecessary health care costs, and is one of the main obstacles in the development of effective preventive pancreatic surgical programs [3, 8]. Clinical decision making in the management of pancreatic IPMNs is currently regulated by a few different guidelines; these are mostly based on diagnostic imaging [9–12], expert opinion, and supported by a low grade of evidence. The addition of endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasonography with fine needle aspirate (EUS-FNA) to conventional radiology only slightly improves the already low diagnostic accuracy, largely impaired by the overall poor accuracy of cytological analysis [3]. Often the only criterion for resection, and consequently any potential for early treatment of pancreatic cancer and its precursor lesions, is radiological assessment and follow-up of patients with IPMN.

European [9] and international [12] guidelines for the management of cystic neoplasms of the pancreas differ in crucial aspects, such as the definition of the main pancreatic duct involvement in IPMNs, although both agree that MPD involvement is associated with a significant increased risk of cancer [9, 10]. Consensus regarding a precise cutoff value for when to regard dilation of the main pancreatic duct (MPD) as secondary to a main duct or mixed-type IPMN, an indication for surgical resection, is currently lacking. In the European guidelines, a MPD ≥ 6 mm is considered an indication for surgery [9], while in the international guidelines, resection is recommended instead when the MPD is ≥ 10 mm [10, 12]. In a large series of patients undergoing pancreatic resection for IPMN, the rate of malignancy for patients with a MPD diameter between 5 and 9 mm was 59.6% [13], thus supporting the more aggressive recommendations in the European guidelines concerning the management of suspected main duct involving IPMNs [14]. In another recent study, a MPD diameter of 7.2 mm was identified as the optimal cutoff value for predicting potential cancerization of IPMN [15].

Although European guidelines recommend the use of serum CA19–9 level as a relative criteria for surgical resection [9], few literature studies support this recommendation [16]. Serum CA19–9 could potentially be a useful, non-expensive, and non-invasive tool in the surveillance of IPMN patients and more studies are needed.

These discrepancies in the surgical indications for the treatment of IPMNs need to be resolved in order to homogenize the management of these patients and to avoid unnecessary resections. Further, the optimal timing of surgery (ideally in patients with high-grade dysplasia) needs to be identified for it to be possible to offer preventive and potentially curative pancreatic surgery with any consistancy [3, 17].

Aim This study aims to correlate preoperative MPD dilation stratified into two groups, one greater than 6 mm and the other greater than 10 mm, and elevated CA19–9 with the presence of advanced findings (HGD or IPMN-associated PDAC) on histological analysis.

Materials and methods

Study design

A single-center hospital-based retrospective study was conducted at Karolinska University Hospital upon local hospital ethical committee approval (EPN 2015/1544–31/4). The study was conducted on a prospectively collected cohort of patients with surgically resected IPMNs of the pancreas. Patient demographics, potential pancreatic cancer risk factors, clinical symptoms, radiological characteristics, and histological results were collected in a standardized fashion by a trained physician.

Cohort and population's characteristics

All consecutive cases of histologically verified IPMNs resected at Karolinska University Hospital from 2008 to

2015 were included in the present study. Patients were followed up with MRI/MRCP. The presence of clinical symptoms (jaundice or IPMN-induced acute pancreatitis), radiological risk factors (main duct dilatation ≥ 6 mm), or presence of mural nodules (mean dimension of the cyst ≥ 4 cm in cases of BD-IPMNs) at the preoperative imaging all constituted surgical indications according to The European Consensus Conference for the Management of Cystic Tumors of the Pancreas (from October 2011) [9]. All cases were discussed in the setting of a multidisciplinary conference prior to surgery and an expert radiologist in the field reviewed the preoperative radiological diagnosis (maximum diameter of the duct, presence of mural nodules, mean diameter of the cyst). The definition of MPD-involving IPMN varies between different guidelines. European guidelines suggest that maximum MPD diameter ≥ 6 mm might imply MPD involvement from IPMN. In international guidelines, maximum MPD diameter ≥ 10 mm is considered high-risk stigmata for pathological involvement of MPD in IPMN. Therefore, we have also performed a sensitivity analysis according to the degree of maximum MPD dilation. Data regarding demographics (age and sex), metabolic data (BMI, presence of diabetes, weight loss), baseline CA19–9 level (greater than 37 μ/ml was considered elevated), final pathological assessment (degree of dysplasia, presence of cancer, TNM, specific histological phenotype), and exposure to known risk factors for pancreatic cancer (smoking, alcohol, obesity) were also collected and analyzed.

Statistical analysis

Chi-squared test was used for categorical variables and Student's *t* test for continuous variables. Mantel-Haenszel test for trend was used to further analyze different subclasses of MPD dilation as ordinal variables. Significant variables were analyzed by sex- and age-adjusted logistic regression analysis. A sex- and age-adjusted multivariable logistic regression analysis was also performed (enter selection procedure) for statistically significant risk factors. The 95% confidence interval (CI) was calculated, all p values were two-sided, and a $p < 0.05$ was considered statistically significant. A statistical software package was used for data analysis (MedCalc Mariakerke, Belgium).

Results

Patient characteristics

Between 2008 and 2015, 152 patients underwent surgical resection for IPMN. Seventy-two patients displayed low-grade dysplasia, 29 HGD, and 51 cancer. The patient's baseline characteristics are summarized in Table 1.

Table 1 Characteristics of IPMN patients

Number of patients	152
Number of male	78 (51.3%)
Mean age (years)	69.04 (67.76–70.31, 95% CI)
Median age (years)	69.67 (68.42–71.30, 95% CI)
BMI	25.72 (24.98–26.45, 95% CI)
Number of smokers	56 (34.2%)
Patients with familial history of pancreatic cancer	4 (2.6%)
Patients with diabetes	37 (24.3%)
Patients with symptoms	49 (32.2%)
Wirsung duct mean size	7.61 (6.64–8.57, 95% CI)
Cyst mean size	30.84 (26.46–35.25, 95% CI)
Multifocal IPMNs	69 (45.4%)
Head localization	63 (41.4%)
Body-tail localization	56 (36.8%)
Diffuse localization	14 (9.1%)
Uncinate localization	19 (12.5%)
Brach duct IPMNs	75 (49.34%)
Main duct IPMNs	19 (12.50%)
Mixed type IPMNs	64 (42.10%)
Patients undergone pancreaticoduodenectomy	79 (51.97%)
Patients undergone distal spleno-pancreatectomy	48 (31.57%)
Patients undergone total pancreatectomy	19 (12.50%)
Enucleations	6 (3.94%)

General risk factors and cyst characteristics

The presence of HGD or IPMN-associated PDAC was not statistically more prevalent in groups of patients with cyst dimension ≥ 40 mm, mural nodules known, or suggested risk factors for pancreatic cancer, such as a clinical history of diabetes mellitus, smoking habit, and family history of pancreatic cancer.

HGD or IPMN-associated PDAC was also not statistically more prevalent in patients with multifocal disease or with specific locations of the cyst (Table 2).

Symptoms

Patients with jaundice displayed a statistically significant higher prevalence of HGD or IPMN-associated PDAC (17.5% vs 1.3%; $p = 0.0009$) (Table 2). At sex- and age-adjusted univariable logistic regression analysis, jaundice was a confirmed to be associated to the presence of HGD or IPMN-associated PDAC (OR 15.3, CI 1.9–121.2, $p = 0.009$) (Table 3).

Table 2 Prevalence of high-grade dysplasia/cancer and low-grade dysplasia according to possible other risk factors

Risk factor	HGD/cancer	LGD	*p* value
Cyst diameter ≥ 40 mm	22/80 (27.5%)	25/72 (34.7%)	0.33
Mural nodules	1/80 (1.2%)	1/72 (1.3%)	0.94
Acute pancreatitis	4/80 (5.0%)	8/72 (11.1%)	0.16
Diabetic patients	23/80 (28.7%)	14/72 (19.4.%)	0.18
Family history of PDAC	2/80 (2.5%)	2/72 (2.7%)	0.91
Multifocal	35/80 (43.7%)	34/72 (47.2%)	0.66
Uncinatus localization	10/80 (12.5%)	8/71 (11.2%)	0.81
Head localization	37/80 (46.2%)	25/71 (35.2%)	0.17
Number of smokers	30/80 (37.5%)	26/72 (36.1%)	0.85
Jaundice	14/80 (17.50%)	1/72 (1.30%)	0.0009
CA19.9 ≥ 37 μ/ml	35/73 (47.9%)	12/68 (17.6%)	0.0001
MPD 1–5.9 mm	26/80 (32.50%)	49/72 (68.05%)	< 0.0001
MPD 6–9.9 mm	32/80 (40.0%)	14/72 (19.44%)	0.006
MPD ≥ 10 mm	22/80 (27.50%)	9/72 (12.50%)	0.02

CA19–9

The presence of HGD or IPMN-associated PDAC was statistically more prevalent among patients with a preoperatively elevated CA19–9 level (47.9% vs 17.6%, $p = 0.0001$) (Table 2). On sex- and age-adjusted univariable logistic regression analysis, an elevated CA19–9 was confirmed to be associated with HGD or IPMN-associated PDAC on histological analysis (OR 4.1, CI 1.9–9.0, $p = 0.0003$) (Table 3). The level of CA19.9 has been evaluated as a continuous variable pooling together HGD/cancer. Increasing levels of the marker are significantly associated with a higher risk of HGD/cancer (OR for every unit increase 1.01, CI 1.00–1.02, $p = 0.003$).

Ca19.9 as a continuous variable is still significantly associated with an increased risk of lone HGD or lone cancer (considered apart one from the other) at sex- and age- adjusted univariable logistic regression analysis, respectively, OR 1.01 (1.00–1.02 95% CI, $p = 0.04$) and OR 1.01 (1.00–1.02 95% CI, $p = 0.03$) for every incremental unit of CA19.9. At multivariable sex- and age-adjusted logistic regression analysis, CA19.9 corrected for jaundice still remains significantly associated to cancer, respectively, OR 1.01 (1.00–1.02 95% CI, $p = 0.008$) for every incremental unit of Ca19.9 and OR 17.94 (2.03–157.98 95% CI, $p = 0.009$) for jaundice.

Table 3 Sex- and age-adjusted univariable logistic regression analysis

Risk factor	OR (95% CI)	*p* value
MPD 6–9.9 mm	OR 2.92, CI 1.38–6.20	0.005
MPD ≥ 10 mm	OR 2.65, CI 1.12–6.25	0.02
Jaundice	OR 15.36, CI 1.94–121.22	0.009
Elevated CA19.9	OR 4.15, CI 1.90–9.05	0.0003

Main pancreatic duct maximum diameter

The presence of LGD, when compared to HGD or IPMN-associated PDAC, was significantly more prevalent in patients with a MPD diameter between 1 and 5.9 mm (68.0% vs 32.5%; $p = 0.0001$). While the presence of HGD or IPMN-associated PDAC, when compared to LGD, was statistically more prevalent when the MPD diameter was between 6 and 9.9 mm (40.0% vs 19.4%; $p = 0.006$) and when the MPD diameter was ≥ 10 mm (27.5% vs 12.5%; $p = 0.02$) (Table 2). The mean diameter of MPD dilation in patients with LGD compared to patients with cancer was significantly different: 7.54 mm (6.26–8.83) vs 7.75 mm (6.34–9.15), $p = 0.03$, as well as it was significantly different the mean diameter of MPD dilation in patients with LGD compared to HGD: 6.14 mm (4.91–7.37) vs 11.02 mm (7.96–14.08), $p = 0.004$.

Using Mantel-Haenszel test for trend HGD or IPMN-associated PDAC was also confirmed to be significantly more prevalent in the subclasses with MPD dilation between 6 and 9.9 mm and those with MPD-dilation ≥ 10 mm (Table 4).

On sex- and age-adjusted univariable logistic regression analysis, a MPD either between 6 and 9.9 mm or ≥ 10 mm was confirmed to be associated with HGD or IPMN-associated PDAC (respectively, OR 2.9, CI 1.3–6.2, $p = 0.005$ and OR 2.6, CI 1.1–6.2, $p = 0.02$) (Table 3). Further, we constructed two different models of sex- and age-adjusted multivariable logistic regression analysis. In the first model we considered the association between a MPD dilation of 6–9.9 mm, jaundice, and an elevated serum CA19–9. These factors were all confirmed to be associated with the presence of HGD or IPMN-associated PDAC on histological analysis (respectively, OR 2.6, CI 1.1–6.0, $p = 0.02$; OR 12.4, CI 1.4–106.9, $p = 0.02$; OR 3.7, CI 1.6–8.4, $p = 0.001$) (Table 5).

In the second model we examined the association between a MPD dilation ≥ 10 mm, jaundice, and an elevated serum CA19–9. In this latter model, jaundice and an elevated serum CA19–9 were found to be associated with the presence of HGD or IPMN-associated PDAC on histological analysis (respectively, OR 8.9, CI 1.0–75.5, $p = 0.04$; OR 3.6, CI 1.6–8.1, $p = 0.001$), while a MPD dilation ≥ 10 mm showed a trend towards statistical significance without reaching it, probably because the sample size was underpowered for this assessment (OR 2.3, CI 0.8–6.2, $p = 0.08$) (Table 6).

Table 4 Prevalence of high-grade dysplasia/cancer and low-grade dysplasia according to different classes of MPD dilation (Mantel-Haenszel test for trend)

Risk factor	HGD/cancer	LGD	*p* value
MPD 1–5.9 mm	26/80 (32.50%)	49/72 (68.05%)	*p* trend < 0.0001
MPD 6–9.9 mm	32/80 (40.0%)	14/72 (19.44%)	
MPD ≥ 10 mm	22/80 (27.50%)	9/72 (12.50%)	

Table 5 First model of sex- and age-adjusted multivariable logistic regression analysis considering MPD diameter between 6 and 9.9 mm, jaundice, and elevated serum levels of CA19.9

Risk factor	OR (95% CI)	*p* value
MPD 6–9.9 mm	2.64, CI 1.15–6.06	0.02
Jaundice	12.43, CI 1.44–106.93	0.02
Elevated CA19.9	3.71, CI 1.63–8.46	0.001

Discussion

The risk of IPMNs progressing to PDAC is well established and increases over time [18], and surgical resection of IPMNs represents the only viable chance at early prevention of pancreatic cancer through preventive surgery available today [3]. Considering the low incidence of pancreatic cancer and the high prevalence of IPMNs in the population, clearly only a minority of these precancerous lesions will progress to cancer. The low accuracy in differentiating between different types of cystic lesions [7, 19, 20], particularly between potentially malignant (i.e., IPMNs) and benign ones (i.e., serous cystic neoplasm) [21], further complicates the clinical decision-making process.

The accurate selection of patients suitable for preventive pancreatic surgery represents one of the largest medical challenges for the future [3]. The clinical dilemma as whether to potentially either unnecessarily recommend a surgical treatment that harbors high morbidity and mortality rates (up to 50% and 6.7%, respectively) [22], or risk offering the conservative management of a lesion that progresses to a decidedly fatal disease like pancreatic cancer [23]. A precise cutoff value able to define the MPD involvement in IPMNs, and thus the ability to identify high-risk lesions suitable for surgical treatment, has not been established. The absence of uniform indications across different guidelines leads either to the risk of surgical mismanagement by either overtreating or undertreating of these patients [7]. In further support of a more aggressive surgical strategy, Hackert et al. [13] have recently reported an association between MPD dilatation between 5 and 9 mm and HGD or IPMN-associated PDAC in up to 59.6% of patients. In addition, Sugimoto et al. recently suggested a cutoff of 7.2 mm to be the best predictor of a malignant neoplasm [15].

Table 6 Second model of sex- and age-adjusted multivariable logistic regression analysis considering MPD diameter ≥ 10 mm, jaundice, and elevated serum levels of CA19.9

Risk factor	OR (95% CI)	*p* value
MPD ≥ 10 mm	2.35, CI 0.88–6.23	0.08
Jaundice	8.96, CI 1.06–75.52	0.04
Elevated CA19.9	3.63, CI 1.61–8.19	0.001

Our study confirms that both MPD dilation between 6 and 9.9 mm and MPD dilation ≥ 10 mm are associated with the finding of HGD or IPMN-associated PDAC on histological analysis. In our analysis we have separated the MPD dilation cutoff 6–9.9 mm from the cutoff ≥ 10 to try to purify the esteem of real risk associated with minor increasing of the duct (6–9.9 mm). Pooling them together would have implied an overesteem of the effect of MPD dilation because at least part of the HGD/cancer cases would have been associated to duct diameter ≥ 10, which already meet criteria for surgery according to European Guidelines for the Management of Cystic Tumors [9].

Interestingly, patients with IPMNs with a main duct diameter ≥ 10 mm had a lower incidence of HGD and invasive cancer (27.5%) when compared to a MPC diameter between 6 and 9.9 mm. The study is probably underpowered to investigate this aspect, which probably is impaired by an intrinsic and unavoidable selection bias. Patients with MPD diameter above 10 mm were numerically less, because most likely have already undergone surgery when displaying less degree of MPD dilation (6 and 9.9 mm) according to European Guidelines for the Management of Cystic Tumors [9].

In the current study, patients were followed up with contrast-enhanced MRI/MRCP since it allows discussion in a multidisciplinary setting and implies the possibility to discriminate between nodules with contrast enhancement from nodules without. EUS was performed as a completing investigation when the conventional radiology was not diriment in a minority of patients and of course that justify the low rate of suspect mural nodules [24].

Elevated serum level of CA19–9 was also associated with advanced finding at final histology, independent of smoking status. This data is in accordance with findings by Fritz et al. [16] and with European Guidelines for the Management of Cystic Tumors [9]. The presence of jaundice is also associated with an increased risk of HGD or IPMN-associated PDAC, although a rare presentation of IPMN. In contrast to what has been reported in the literature, no association was found between more advanced histology and the diameter of the cyst, which based on our findings cannot be recommended as an absolute criteria for resection [25].

In the current study increased value of CA19.9 and jaundice have been associated to increased risk of cancer and HDG. We considered the possibility that jaundice itself could represent a possible cause of increased CA19.9 level. Among the 29 patients with HGD, 8 (27.58%) had even increased CA19.9. In this subgroup, 2 (6.89% of the total) displayed concomitant jaundice. CA19.9 displayed a linear association (when considered as continuous variable) with

HDG, cancer, and HGD/cancer pooled together. Thus, jaundice and elevated CA19.9 probably represent two independent, non-collinear, features associated with the finding of a more lesions at final histology. At multivariate logistic regression analysis, elevated CA19.9 remains significantly associated with the occurrence of cancer and HGD/cancer even if corrected for jaundice.

The presence of HGD or IPMN-associated PDAC was not statistically more prevalent in groups of patients with other possible risk factors as mean cyst size ≥ 40 mm or the presence of mural nodules. This is probably due to the low power of current study in investigating these features, which probably occur later in the natural history of IPMN, as compared to minor dilation of the MPD (6–9.9 mm). Therefore, at least part of the patients met surgical criteria for resection due to less degree of MPD dilation, before the appearance of mural nodules or cyst dimension ≥ 40 mm. We also pooled together MPD involving IPMNs (mixed-type and pure main duct IPMNs) because the preoperative assessment of the MPD dilation can hardly discriminate between primitive and secondary dilation (due to possible compressive factors from the cystic lesion).

The study aimed at investigating the weight of specific preoperative features possible associated to higher risk of displaying HGD/cancer at final histology, in a real-life population meeting surgical criteria (including patients with large BD-IPMN and normal MPD). As every study, even this has some limitations, such as the retrospective collection of data and the possible presence of selection and systematic biases. On the other hand, it has some strengths too, particularly regarding the strict inclusion criteria (histologically proved IPMNs), and the preoperative and postoperative high diagnostic accuracy (all diagnosis were, respectively, reviewed by pathologist and by a radiologist expert in pancreatic diseases).

Finally, this is one of the few studies specifically proposing preoperative features able to distinguish lesions amenable for surgery and therefore proposing a radical management change for IPMN patients.

In conclusion, our study shows the importance of MPD dilatation in IPMNs and stresses that even a minor (6–9.9 mm) dilatation of the MPD can be associated with a significant risk of HGD or IPMN-associated PDAC and therefore necessitates surgical resection. As the aim of pancreatic surgery is achieving the highest level of oncological radicality as possible, then we suggest the use of a cutoff between 6 and 9.9 mm to detect precursor lesions that are suitable for surgical treatment. Larger, preferably multi-center studies are strongly needed to identify signs and markers that may be used to optimize surgical timing as to prevent pancreatic cancer by treating patients early and therefore definitively and significantly impact its dire prognosis.

Author's contributions Zeeshan Ateeb collected the data and contributed to write the manuscript. Roberto Valente contributed to write the manuscript and performed the statistical analysis. Yasmine Schlieper contributed to collect data. Carlos Fernaned Moro revised the patient's histology. Raffaella M. Pozzi-Mucelli revised the patient's radiological files. Linnea Malgerud, Elena Rangelova, Johannes Matthias Löhr, and Urban Arnelo critically revised the manuscript. Marco Del Chiaro was responsible of the study design and contributed to write the paper.

Funding The present study was supported by Cancerfonden, Sweden (CAN 2014/634 and CAN 2014/621) and ALF Medicine (2016 #20150113).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval was obtained by the local ethical committee (EPN 2015/1544–31/4).

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