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Conflict of interest: Authors declare no conflict of interest for this work.

No funding source was involved for this study.

Authors contribution: S.O. conducted the data extraction and wrote the manuscript. J.I conducted the data extraction. C.M. conducted the original draft preparation. C.H. conducted the original draft preparation and the data extraction. L.O. conducted the original draft preparation and the data extraction. V.L. conducted the original draft preparation and the data extraction. E.R. conducted the original draft preparation and the data extraction. L.D. conducted the original draft preparation and the data extraction. H.C. conducted the original draft preparation and the data extraction. P.FD. conducted the original draft preparation and the data extraction. O.G. conducted the original draft preparation and the data extraction. J.U. conducted the original draft preparation and the data extraction. Y.K. conducted the original draft preparation and the data extraction. S.B. conducted the original draft preparation and supervised the project. C.T. conducted the original draft preparation and supervised the project. Y.D. conducted the data analysis and supervised the project. All the authors reviewed the manuscript and approved the final draft.

Abstract

Objectives: Obesity is known to be both a major risk factor for endometrial cancer and associated with surgical complexity. Therefore, the management of these patients is a challenge for surgeon and oncologist. The aim of this study is to assess the adherence to ESGO guidelines in patients morbidly obese (BMI > 40 kg/m2). The secondary objectives were the impact on overall survival and recurrence free survival.

Methods: All the patients who were treated for an EC in the 11 cancer institutes of the Francogyn group were included and classified into 3 weight groups: morbid (MG) (BMI over 40kg/m2), obese (OG) (BMI between 30 and 40kg/m2) and normal or overweight (NOG) (with a BMI under 30kg/m2). Adherence to guidelines was evaluated for surgical management, lymph node staging and adjuvant therapies.

Results: 2375 patients were included: 1330 in NOG group, 763 OG group and 282 in MG group. The surgical management of MG was in according with the guidelines in only 30% of cases against 44% for OG and 48% for NOG (p< 0.001), especially because of a lack of lymph node staging. MG were more likely to receive the recommended adjuvant therapy (61% for MG, 52% for OG and 46% for NOG, p-value under 0.001).

Weight had no impact on OS (p-value=0.6) and MG patients had a better RFS (p =0.04).

Conclusion: Adherence to international guidelines for surgical management is significantly lower in MG patients, especially the procedures of lymph node staging. However, MG patients had more often the adequate adjuvant therapies. MG patients had a better RFS probably because of better prognosis tumors.

Keys message:

What is already known on this topic: Obesity is a risk factor of endometrial cancer. Its impact on the management of patients is however still debated.

What this study adds: The surgical management of patients with severe obesity is significatively different than the guidelines. However, severe obese patients have a better RFS and no impact was found on OS.

How this study might affect research, practice or policy: The development of robotic surgery, the extension of SLN indications and the study of new biological markers might improve the management of severe obese patients.

Key words: Endometrial cancer; severe obesity; clinical management; morbid obesity; sentinel lymph node; minimally invasive surgery

Introduction

Endometrial cancer (EC) is the sixth most frequently diagnosed cancer in women, with 417.000 new cases and 97.000 new deaths in the world in 2020(1). The increasing number of cases in western countries could reflect the significant proportion of patients with risk factors such as obesity(2). According to the WHO, patients with excessive body mass index (BMI) over 25 kg/m^2 may represent two billions of people, or 30% of the world population(3). In this population, the relative risk to developpe an endometrial cancer is ranging from 2.7 for patients with a BMI higher than 30 kg/m^2 to 4.7 for those with a BMI higher than 35 kg/m^2(2).

Surgery and adjuvant therapy for EC are determined according to ESGO-ESMO-ESTRO guidelines(4). Many reports previously described the surgical complexity of managing obese patients, usually at increased risk of post operative complications(5). Vargiu and al. recently showed that obese patients were under-staged in 9.4% of cases (p=0.017) because of sentinel lymph node (SLN) failure(6). Wissing M and al. showed that successful SLN or pelvic lymphadenectomy (LND) correlated negatively with BMI levels (adjusted OR 0.86 CI95% [0.76–0.97] for SNL and 0.76 CI95% [0.59–0.96] for LND, per 1 kg/m2 increment)(7).

Likewise, dealing with severe obesity is a challenge for oncologists. Furlanetto et al. showed in a prospective randomized trial that obese patients who received the real dose dense chemotherapy according to their weight without adjustment had more severe toxicities without impact on survival(8). In the same time, ESGO guidelines clearly advise full dose chemotherapy to avoid under treated patients(9) .

In this context, clinicians always balance the need to offer obese patients the most appropriate therapies with the significant increase in morbidity in this population.

123 The primary objective of this study was to assess the adherence to ESGO guidelines in
124 patients morbidly obese (BMI > 40 kg/m2). Our secondary objective included survival
125 analysis stratified by BMI categories.
126

Methods

Population included

The research protocol was approved by the institutional review board of the French College of Obstetrics and Gynecology (2023 – GYN – 0108).

The inclusion was retrospective and multicentric, including 11 French tertiary cancer institutions of the FRANCOGYN group: Creteil University Hospital, Jean Verdier University Hospital, Lille University Hospital, Poissy University Hospital, Tenon University Hospital, Tours University Hospital, Rennes University Hospital, Reims University Hospital, Clermont-Ferrand University Hospital, Brest University Hospital, and Jean-Francois Leclerc Hospital. Patients treated for an EC histologically proven between 2000 and 2020 in one of the involved centers were selected.

Patients with BMI < 18 kg/m^2, advanced metastatic disease never operated, rare tumors and incomplete anamnesis or follow up (lack of information on age, BMI or histology) were excluded.

Data collection

The following data were abstracted from patients' chart: socio-demographic, BMI (calculated as the weight in kilograms divided by the square of the height in meters, both measured at the time of diagnosis, and expressed in kg/m2), parity, menopausal status, high blood pressure, diabetes, hormone replacement therapy, history of breast cancer, FIGO stage, final pathologic analysis and adjuvant therapy. The date of surgery, recurrence and death were also reported.

Patients' management

Preoperative work-up included a digital vaginal and speculum examination, ultrasound, and pelvic MRI to assess preoperative risk group. All patients managed before the actualization of ESMO guidelines were re-evaluated to determine preoperative risk of lymph node invasion.

Patients' management were theoretically based on ESGO guidelines (4) and systematically validated in multidisciplinary committee including at least a radiologist, a onco-gynecological surgeon, a pathologist, and a medical oncologist.

The surgical treatment consisted of a hysterectomy with bilateral salpingo-oophorectomy(4,10). The lymph node staging of patients treated before 2016 was considered to be in adequation with guidelines if patients underwent a pelvic LND or a SLN for low-risk group and if it was associated with a lombo-aortic lymphadenectomy for intermediate and high group risk(10). After 2016, the lymph node staging was concordant only if a SLN was performed for low risk and a pelvic and lombo-aortic lymphadenectomy for intermediate and high group risk(4).

Tumors were classified according to the FIGO 2018 classification after final pathologic analysis(11).

Adjuvant therapy was assessed according to the postoperative group of risk of recurrence(4).

Evaluation of the adherence to guidelines

The concordance of the surgical procedure and the indication of adjuvant therapy was evaluated separately. The global management was considered to be concordant if the surgical and the adjuvant therapy was concordant to guidelines.

In all centers, for patient with stages I or II cancer, the follow up visit was conducted every six months for five years then every year with a simple clinical exam. For patients with stage III or IV cancer, follow-up visits were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

Statistical analysis

Data were managed with an Excel database (Microsoft Corporation, Redmond, WA, USA) and analyzed using SAS v9.4 (SAS Institute, Cary, NC, USA).

Patients were retrospectively divided into three groups according to their BMI: normal, obese and morbid. “Normal or Overweight group” (NOG) included patients with a BMI greater or equal than 18 and less or equal than 30. “Obese group” (OG) included patients with a BMI higher than 30 but lower than 40. Eventually, "morbid group” (MG) included grade 3 obesity, also known as severe obesity, defined as a BMI higher than forty.

Statistical analysis was based on Chi square and Fisher’s exact tests for ordinal variables. For continuous variables, Student’s t test or Mann-Whitney test were used (p values < 0.05 were considered significantly different). Recurrence free survival (RFS) was defined as the time between surgery and relapse or the last follow up if no event occurred. Overall survival (OS) was calculated from the date of surgery to death or the last follow up if no event occurred. Patients who were still alive or without recurrence were censored at the date of the last follow-up visit. The Kaplan-Meier method was used to estimate the survival distribution and the log-rank test was used to compare survival data (p values < 0.05 were considered significantly different).

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

Results

Characteristics of the study population

Between 2000 and 2020, 2852 patients were treated for an EC within one of the centers involved and 2375 were selected for analyses (Figure 1). NOG patients represented 1330 patients, OG 763 patients and MG 282 patients.

The main characteristics of the patients are displayed in Table 1.

MG patients were significatively younger with a median age of 63 for MG, 66 for OG and 68 for NOG (p-value < 0.001) and had more comorbidities as high blood pressure (181 (64%) MG patients,392 (51%) OG patients, 445 (33%) NOG patients (p-value < 0.001)) or diabetes (109 (39%) MG patients,188 (25%) OG patients and 131 (10%) NOG patients (p-value < 0.001)).

MG patients had less aggressive tumor than OG or NOG patients. Endometrioid carcinoma represented 238 (88%) MG tumors, 634 (85%) OG tumors and 1054 (81%) NOG tumors (p-value= 0.002). Among them 150 (63%) were grade 1 for MG, 359 (57%) for OG and 555 (53%) for NOG tumors (p-value=0.005). Therefore, MG patients were more often classified in low ESMO group than OG or NOG patients (141 (52%), 296 (40%) and 496 (38%) respectively, p-value < 0.001).

Adherence to guidelines according to BMI group.

Adherence to guidelines according to BMI group are displayed in table 2.

MG patients were managed according to guidelines in 19% of cases (53 patients) against 24% of NOG or OG patients (322 and 182 patients respectively) (p-value = 0.138).

The surgical management of MG patients was more likely different from guidelines for low and intermediate group risk than high group risk (Table 3).

The surgical route chose for low and intermediate group risk was more often laparoscopic for NOG and OG. For MG patients open surgery was more often elected (p-value < 0.001).

MG patients had significatively less lymph node staging when indicated. 85 (30%) MG patients had the recommended surgical management against 644 (48%) NOG patients and 355 (44%) OG patients (p-value < 0.001).

MG patients had less often SLN biopsy when required. Only 16 (11%) MG patients versus 70 (24%) OG patients and 153 (31%) NOG patients had a SLN in low group (p-value < 0.001 for low risk and p-value=0.005 for intermediate). Furthermore, when it was performed, only 10 (63%) SLN was detected in MG patients versus 62 (89%) in OG and 137 (90%) in NOG (p-value=0.008).

Pelvic LND was less often performed in MG patients at low and intermediate group risk. 24 (7%) MG patients versus 111 (57%) OG patients and 211 (65%) NOG patients had a pelvic LDN in intermediate group (p-value=0.002 for intermediate and p-value < 0.001 for low risk).

In high group risk, there was no significant difference between weight groups for surgical approach or pelvic lymph node staging. MG patients had less para-aortic lymphadenectomy (16 (23%) MG patients, 90 (35%) OG patients and 197 (41%) NOG patients, p = 0.011).

In all weight groups, the weight had not impact on lymph node invasion on final pathology.

Adjuvant therapy

171 (61 %) MG patients were managed according to guidelines for adjuvant therapy while only 396 (52%) OG patient and 618 (46 %) NOG patients had the adjuvant therapy recommended (p < 0.001). In the sub-group analysis, no significative trend was observed.

Survival analysis

The survival curves are displayed in figure 2. Mean follow up was 40 months. MG patients had a better RFS than OG and NOG (p = 0.04). No difference was observed in OS (p = 0.6). Survival curves comparing morbide obese patients to the obese and non-obese or overweight patients are displayed in Supplementary Figure 1.

Discussion

Summary of main results

In our retrospective multicentric cohort, we found that MG patients were more likely to have an incomplete or inappropriate lymph node staging, even in low and intermediate risk situations. Indeed, 70% of MG patients didn't have the recommended staging when only 56% of OG patients and 52% of NOG patients' staging were not in accordance to guidelines ($p < 0.001$). However, the choice of adjuvant therapy was more often in accordance with guidelines: 61% of MG patients and only 52% of OG patients and 46% of NOG patients ($p < 0.001$). MG patients had increased RFS when compared to OG or NOG ($p=0.04$), but without significant impact on OS ($p=0.6$).

Results in the context of published literature

Severe obesity is associated with surgical complexity, especially for lymph node staging. Vargiu et al. reported that obese patients (BMI>35kg/m2) were under-staged during EC management in 9.4% versus 5% of non-obese patients (p-value=0.017). Moreover, there was an empty package dissection in 8.2% of cases versus 3.9% for non-obese patients (p-value=0.022)(6). Canlorbe et al. highlighted that nodal staging was performed for only 70% of obese patient in high group risk against 90% of non-obese patients (p-value<0.0001) and it was associated with a poorest RFS (HR=12.5 CI95%[3.1-51.3])(12). In our cohort, MG patients had significantly less lymph node staging, and this was even significant for pelvic lymph nodes in the low and intermediate group risk. For high group risk, the difference was observed on para-aortic staging ($p = 0.011$).

The generalization of SLN, especially for high-risk patients, might improve the lymph node staging in patients with EC. The FIRES trial showed a sensitivity to detect node-positive

disease of 97.2% (CI95% [85.0-100]), and a negative predictive value of 99.6% (CI95% [97.9–100]) even for high group risk(13). This procedure has been especially studied for obese patient by Matanes et al. who showed that performing a SLN instead of a pelvic LDN for obese patients is associated with a shorter operative time ($p < 0.001$) and less blood loss ($p = 0.03$) without impact on OS and RFS (p 0.7 and 0.4 respectively)(14). SLN procedures in high-risk obese patients could increase the proportion of patients benefitting from the appropriate surgical and adjuvant therapies according to ESGO guidelines.

Regarding survival, the impact of obesity remains unclear. In a meta-analysis by Kokts-Porietis RL and al, the increase of the BMI is associated with a higher cancer recurrence and all-cause mortality but no impact was found on cancer specific mortality(15). In our cohort, MG patients had a better RFS ($p=0.04$) but without difference in OS between weight group ($p=0.6$). This difference in RFS could be explained by the fact that morbid obesity seems to be associated with better prognostic tumors: more endometrioid carcinoma, lower FIGO stage and therefore more low-risk group (p-value under 0.001). In this group risk, the probability of lymph node invasion is lower so the lack of lymph node staging had probably less impact on RFS.

MG patients were also younger than OG or NOG patients (median of 63, 66 and 68 years old respectively, p-value under 0.001) which could impact positively OS.

The development of quality indicators by ESGO and the certification of care centers might improve the adherence of international guidelines (16). Adherence to guidelines was more important regarding the choice of adjuvant therapy in obese patients, without significative difference after further stratification. The recent inclusion of the molecular analysis including immunohistochemistry for p53, mismatch repair proteins, and DNA sequencing for POLE exonuclease domain aim to tailor adjuvant therapies according to

specific subgroups. For example, simple clinical surveillance can be decided in POLE-mutated patients(4). Vanessa M López-Ozuna and al. has already been working on finding molecular predictive biomarkers for obese patients(17). Finding the molecular marker that enables to avoid the surgical difficulties in this population seems to be the next big thing. In the present cohort, the impact of molecular classification couldn't be evaluated because of the lack of information for all patients due to our inclusion period.

Strengths and weaknesses

Some of the limits deserve to be mentioned. The retrospective nature of our work could have biased the results. However, the large multicentric inclusion reflect the difference of management of EC in several French cancer institutions.

Furthermore, due to the large time of inclusion (2000 to 2020), few patients have been operated by robotic access. E. Kawai and al. showed that obese patients can safely undergo robotic access surgery compared to non-obese patients with no more laparotomy conversion (5% vs 3% p-value 0.619) or post operative complications (5% vs 9%, p-value 0.738). However, despite the use of robotic assisted laparoscopy, less obese patients underwent pelvic lymphadenectomy (5 vs 12%, p-value=0.005)(18). Moreover, indications for lymph node surgical staging evolved over the years with more patients eligible to less morbid procedures such as SLN. However, a strength of this work was that the adherence to guidelines was evaluated according to the year of management for each patient included.

Another lack of this study is the absence of information regarding post operative complications. It remains possible that the occurrence of some complications had impact on the decision to propose adjuvant therapies. Laparotomy surgical access is significatively more chosen in MG population (22% of MG patients against 17% of NOG patients in low

group risk (p-value of 0.001); 45% of MG patients against 22% of NOG patients in intermediate group risk (p-value of 0.001). Bouwman and al. showed that obese women had significantly more postoperative surgical complication mainly if the access is open surgery(5). Reijntjes et al. showed in a randomized trial that there were no significative difference between laparoscopy or laparotomy surgical access on RFS (90.3% vs 84.1% CI95% [0.31-1.52]) or OS (89.2% vs 82.8% CI95%0.30-1.19])(19).

Conclusion

Adherence to international guidelines for surgical management but not adjuvant therapies, is significantly lower in morbid obese patients, especially the procedures of lymph node staging.

Recent implementation of sentinel lymph node procedure even in high-risk patients as well as the use of robotic procedures could increase the proportion of patients benefitting from recommended therapies.

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Table 1: Epidemiological and pre operative histological characteristics by body mass index in the whole population.

	NOG N=1330	OG N=763	MG N=282	p-value
Epidemiological charecteristics :				
Age, mean (median)	67 (68)	66 (66)	63 (63)	**< 0.001**
Body mass index, mean (median)	24 (24)	34 (33)	46 (46)	**0.001**
Menopause, n (%)	1223 (92%)	702 (92%)	250 (89%)	0.169
Menopausal hormone replacement therapy, n (%)	292 (22%)	87 (11%)	13 (5%)	**0.001**
High blood pressure, n (%)	445 (33%)	392 (51%)	181 (64%)	**0.001**
Diabete, n (%)	131 (10%)	188 (25%)	109 (39%)	**0.001**
Breast cancer history, n (%)	120 (9%)	52 (7%)	10 (4%)	**0.004**
Nulligravida, n (%)	402 (30%)	226 (30%)	89 (32%)	0.831
Histological charecteristics :				
Histological type, n (%)				**0.002**
Endometrioid carcinoma	*1054 (81%)*	*634 (85%)*	*238 (88%)*	
Other type	*254 (19%)*	*114 (15%)*	*31 (12%)*	
NA	*22*	*15*	*13*	
Histological grade, n (%)				**0.005**
1	*555 (53%)*	*359 (57%)*	*150 (63%)*	
2	*361 (34%)*	*187 (30%)*	*72 (30%)*	
3	*138 (13%)*	*881 (14%)*	*16 (7%)*	
NA	*276*	*129*	*44*	
FIGO stage, n (%)				0.149
IA	*661 (51%)*	*368 (49%)*	*157 (58%)*	
IB	*376 (29%)*	*28 (29%)*	*70 (26%)*	
II	*84 (6%)*	*40 (5%)*	*14 (5%)*	
IIIA	*50 (4%)*	*23 (3%)*	*6 (2%)*	
IIIB	*7 (1%)*	*10 (1%)*	*0 (0%)*	
IIIC	*85 (7%)*	*57 (8%)*	*15 (6%)*	
IV	*45 (3%)*	*32 (4%)*	*7 (3%)*	
NA	*22*	*15*	*13*	
ESMO group, n (%)				**< 0.001**
Low	*496 (38%)*	*296 (40%)*	*141 (52%)*	
Intermediate	*486 (37%)*	*257 (34%)*	*70 (26%)*	
High	*326 (25%)*	*195 (26%)*	*58 (22%)*	
NA	*22*	*15*	*13*	

Table 1: Epidemiological and pre operative histological characteristics by body mass index in the whole population.

MG, morbid group; NOG, non-obese overweight group; OG, obese group.

Table 2: Adherence to guidelines according to weight group

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	NOG N=1330	OG N=763	MG N=282	p-value
Surgical procedure concordance, n (%) :				
	644 (48%)	*355 (44%)*	*85 (30%)*	**< 0.001**
Adjuvant therapy concordance, n (%) :				
	618 (46%)	*396 (52%)*	*171 (61%)*	**< 0.001**
Global adherence, n (%) :				
	322 (24%)	*182 (24%)*	*53 (19%)*	0.138

Table 2: Adherence to guidelines according to weight groups.

MG, morbid group; NOG, non-obese overweight group; OG, obese group.

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Table 3: Surgical procedure by ESMO pre operative group risk of lymph node invasion and by body mass index.

ESMO group risk :	Low				Intermediate				High			
	NOG N = 496	OG N = 296	MG N = 141	p-value	NOG N = 326	OG N = 195	MG N = 58	p-value	NOG N = 486	OG N = 257	MG N = 70	p-value
Surgery												
Surgical route				**< 0.001**				**< 0.001**				0.121
Laparoscopy, n (%)	*394 (79%)*	*226 (76%)*	*92 (65%)*		*247 (76%)*	*145 (74%)*	*24 (41%)*		*255 (52%)*	*118 (46%)*	*33 (47%)*	
Open surgery, n (%)	*86 (17%)*	*56 (19%)*	*31 (22%)*		*73 (22%)*	*36 (18%)*	*26 (45%)*		*211 (43%)*	*127 (49%)*	*29 (41%)*	
Vaginal surgery, n (%)	*11 (2%)*	*10 (3%)*	*15 (11%)*		*2 (1%)*	*8 (4%)*	*4(7%)*		*10 (2%)*	*5 (2%)*	*4 (6%)*	
Robotic laparoscopy, n (%)	*5 (1%)*	*4 (1%)*	*3 (2%)*		*4 (1%)*	*6 (3%)*	*4 (7%)*		*10 (2%)*	*7 (3%)*	*4 (6%)*	
Sentinel lymph node procedure												
Performed, n (%)	*153 (31%)*	*70 (24%)*	*16 (11%)*	***< 0.001***	*113 (35%)*	*56 (29%)*	*8 (14%)*	***0.005***	*69 (14%)*	*25 (10%)*	*6 (9%)*	*0.129*
Detected, n (%)	*137 (90%)*	*62 (89%)*	*10 (63%)*	***0.008***	*109 (96%)*	*51 (91%)*	*7 (88%)*	*0.249*	*56 (81%)*	*23 (92%)*	*6 (100%)*	*0.244*
Positive, n (%)	*10 (7%)*	*6 (10%)*	*2 (20%)*	*0.361*	*21 (19%)*	*8 (16%)*	*1 (14%)*	*0.831*	*15 (27%)*	*9 (39%)*	*1 (17%)*	*0.427*
Pelvic Lymphadenectomy												
Performed, n (%)	*271 (55%)*	*144 (49%)*	*31 (22%)*	***< 0.001***	*211 (65%)*	*111(57%)*	*24 (7%)*	***0.002***	*350 (77%)*	*179 (70%)*	*41 (59%)*	*0.07*
Positive, n (%)	*9 (3%)*	*2 (1%)*	*0 (0%)*	*0.316*	*15 (7%)*	*9 (8%)*	*2 (8%)*	*0.937*	*350 (77%)*	*179 (70%)*	*41 (59%)*	*0.07*
Pelvic staging												
Performed, n (%)	*327 (66%)*	*175 (59%)*	*45 (32%)*	***< 0.001***	*251 (77%)*	*130 (32%)*	*27 (47%)*	**< 0.001**	*359 (74%)*	*188 (73%)*	*45 (64%)*	*0.239*
Positive, n (%)	*15 (3%)*	*8 (3%)*	*2 (1%)*	*0.581*	*33 (10%)*	*16 (31%)*	*3 (5%)*	0.429	*99 (20%)*	*59 (23%)*	*13 (19%)*	*0.620*
Lombo-aortic lymphadenectomy												
Performed, n (%)	*39 (8%)*	*19 (6%)*	*1 (1%)*	***0.009***	*61 (68%)*	*27 (14%)*	*2 (3%)*	***0.009***	*197 (41%)*	*90 (35%)*	*16 (23%)*	***0.011***
Positive, n (%)	*5 (13%)*	*3 (16%)*	*0 (0%)*	*0.880*	*9 (15%)*	*2 (7%)*	*1 (50%)*	*0.197*	*56 (28%)*	*23 (26%)*	*6 (38%)*	*0.607*

Table 3: Surgical procedure by ESMO pre operative group risk of lymph node invasion and by body mass index.

MG, morbid group; NOG, non-obese overweight group; OG, obese group.