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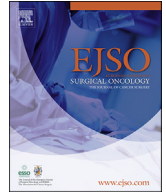
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Misdiagnosis of appendiceal neoplasms as ovarian tumors: Impact of prior gynecologic surgery on definitive cytoreduction and HIPEC[☆]



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ABSTRACT

Background: Female patients with pelvic/adnexal masses often undergo gynecologic operations due to presumed ovarian origin. The diagnosis of an appendiceal tumor is often only made postoperatively after suboptimal cytoreduction has been performed. We hypothesized that an index gynecological procedure increases the morbidity of definitive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in patients with appendiceal mucinous tumors.

Methods: A single-center retrospective review was performed to identify female patients undergoing CRS/HIPEC for appendiceal tumors from 2012 to 2020.

Results: During the 8-year period, CRS/HIPEC was performed in 36 female patients with appendiceal mucinous tumors. Eighteen patients (50.0%) had received a prior pelvic operation by gynecologists (PPO Group) for presumed ovarian origin before referral for definitive CRS/HIPEC. The median peritoneal cancer index (PCI) was higher in the PPO group (21 vs. 9, $p = 0.04$). The median number of days from gynecologic procedure to definitive CRS/HIPEC was 169 days. Compared to patients who did not undergo a prior gynecologic operation, those in the PPO group had higher intraoperative blood loss (650 vs 100 mL, $p < 0.01$) during CRS/HIPEC as well as longer length of stay (12 vs 8 days, $p = 0.02$) and higher overall morbidity (72.3% vs 33.3%, $p = 0.02$). After controlling for PCI, prior gynecologic operation increased risk of 30-day morbidity after definitive CRS/HIPEC (OR 11.6, $p < 0.01$).

Conclusion: A multi-disciplinary approach is needed for the primary evaluation of patients with pelvic masses of undetermined origin. A gynecological resection is associated with increased morbidity during definitive cytoreduction and HIPEC for appendiceal mucinous tumors.

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1. Introduction

Pelvic tumors in female patients are often presumed to be of ovarian origin [1,2]. Gastrointestinal (GI) malignancies are less frequent and make the diagnosis difficult for appendiceal tumors due to the rarity of the pathology and difficulties with diagnosis

based on endoscopic and radiographic findings. Appendiceal tumors, however, commonly present as a pelvic mass with female predominance and have a tendency for ovarian involvement [3,4]. Many of these patients then undergo index gynecologic operations, where the diagnosis of an appendiceal mucinous tumor is often only made after suboptimal debulking for appendiceal histology

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has been performed [5,6]. This approach can lead to a delay in the definitive treatment of appendiceal mucinous tumors with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) [7]. Additionally, subsequent surgery is more challenging due to disruption of anatomic planes and formation of adhesions and scar tissue [7,8]. The delay in definitive treatment and increasing difficulty of CRS/HIPEC can lead to worse outcomes. Therefore, we hypothesized that a prior gynecological procedure increases the morbidity of definitive CRS/HIPEC for appendiceal mucinous tumors.

2. Material and methods

All female patients with appendiceal mucinous tumors who underwent CRS/HIPEC from 2012 to 2020 were identified from a prospectively collected institutional database. Institutional review board approval was obtained for this study from the University of California, Irvine. CRS/HIPEC was performed by one of two colorectal surgeons at a single institution using standard procedural technique. Chemotherapy used was intravenous 5-fluorouracil with leucovorin and intraperitoneal oxaliplatin for 30 min or Mitomycin C for 90 min.

Patients who had undergone an index prior pelvic operation by gynecology for presumed ovarian neoplasm were identified (PPO group) and compared to patients without previous gynecologic operation. Categorical data were reported as percentages and continuous data were reported with median and interquartile range (IQR). Demographics and outcomes were compared between the two groups using Chi Square and Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. Demographics and clinical characteristics included age, race, body mass index (BMI), comorbidities, neoadjuvant and adjuvant chemotherapy, peritoneal cancer index (PCI), pathologic diagnosis of either mucinous appendiceal neoplasm or mucinous appendiceal adenocarcinoma, grade of tumor, and high risk (signet ring) features. Days between initial tissue diagnosis of appendiceal tumor to date of first neoadjuvant chemotherapy infusion or definitive CRS/HIPEC were also calculated. Additionally, prior surgical score (PSS) was calculated for each patient and was defined as PSS-0: no surgery or biopsy only; PSS-1: resection of 1 abdominopelvic region; PSS-2: resection of 2–5 abdominopelvic region; or PSS-3: resection of >5 abdominopelvic regions [9].

The primary outcome was 30-day morbidity, which was defined as having one or more of the following complications: unplanned return to operating room, sepsis, intraabdominal abscess, skin infection, wound dehiscence, *Clostridium difficile* infection, urinary tract infection, pneumonia, reintubation, anastomotic leak, ileus, acute kidney injury, deep venous thrombosis or pulmonary embolism. Morbidity was also classified using Clavien Davido classification (CDC) complication grade. Comprehensive comorbidity index (CCI), which transforms CDC grades into continuous scale from 0 (no complication) to 100 (death), was also calculated [10]. Secondary outcomes included length of operation, estimated blood loss in operation, intraoperative transfusion requirements, length of stay (LOS), intensive care unit (ICU) days, ventilator days, transfusion requirements within first 24 h, readmission within 30 days, recurrence of cancer, and mortality. Length of follow-up was calculated for each patient and was defined as time between date of CRS/HIPEC by colorectal surgery to date of last follow-up. Additionally, progression-free survival (PFS) was calculated as days from date of CRS/HIPEC by colorectal surgery to date of noted recurrence or cutoff date, whichever came first. No patients were lost to follow-up.

Regression models were used to model post-operative outcomes length of hospital stay, length of ICU stay, morbidity,

mortality and complications during and after operation. A univariable logistic regression was performed to evaluate the effect of prior gynecologic surgery on postoperative morbidity after definitive CRS/HIPEC. The main predictor of interest was prior gynecologic surgery. We adjusted for potential confounder, PCI using multivariable logistic regression model. The adjusted risk for morbidity was reported with an odds ratio (OR) and 95% confidence intervals (CI). All p-values were two sided, with a statistically significant level of <0.05. All analyses were performed using SAS 9.4 software (SAS institute Inc, Cary, NC, USA).

3. Results

3.1. Patient demographics

Between November 2012 and December 2020, 36 female patients underwent CRS/HIPEC for appendiceal neoplasms. Of these 36 patients, 18 patients had undergone index pelvic operation for presumed ovarian malignancy by gynecologic oncology (PPO group). Of the 18 patients in the PPO group, 13 patients presented with abdominal complaints of either increased girth, bloating, or pain; 1 patient presented with vaginal bleeding; and 4 patients presented after incidental findings on imaging. 15 of these patients had preoperative computed tomography (CT) scans, of which 8 showed a pelvic mass and 7 showed an adnexal mass. The patient presenting with vaginal bleeding did not have a preoperative CT scan. Prior pelvic operations performed by gynecologic oncology are listed in Table 1, with bilateral salpingo-oophorectomy and appendectomy being the most commonly performed. The median number of days from gynecologic procedure to definitive CRS/HIPEC was 169 days.

The median age, race, BMI, and comorbidities of patients who underwent gynecologic operation first was not significantly different between the two groups (Table 2). The presenting CEA and CA-125 were not different between the groups but were not recorded in 12 and 16 patients, respectively. The PSS differed between the groups, with the PPO cohort having a higher proportion of patients with PSS >1 (77.8% vs 17.7%, $p < 0.01$). The median days from tissue diagnosis to either first infusion of neoadjuvant chemotherapy or definitive HIPEC/CRS was longer in the PPO group, but the difference was not statistically significant (3.7 months vs. 2.6 months, $p = 0.70$). The median PCI was higher in the PPO group (21 vs 9, $p = 0.04$). Forty-two percent of the study population had a pathologic diagnosis of mucinous appendiceal neoplasm, while the other 58% had diagnosis of mucinous appendiceal adenocarcinoma. A lower proportion of patients in the PPO group had mucinous appendiceal adenocarcinomas (38.9 vs 77.8%, $p = 0.04$), high grade tumors (0% vs 22.2%, $p = 0.10$). No patients had positive lymph node status in the study.

3.2. Risk of morbidity associated with prior gynecologic operation

Having a prior gynecologic operation substantially increased the risk of morbidity of definitive CRS/HIPEC with an OR of 9.1 ($p < 0.01$). The most common postoperative complication was ileus (11 patients), followed by intraabdominal abscess (6 patients), wound infection (4 patients), *Clostridium difficile* infection (2 patients), urinary tract infection (4 patients), and pneumonia (3 patients). The PPO group had higher overall morbidity (72.3% vs. 33.3%, $p = 0.02$). CDC grade I/II complications were not different between the groups; however, the proportion of patients with CDC grade III/IV complications was higher in the PPO group (39.0% vs. 11.1%, $p = 0.05$). Three patients in the PPO group required unplanned return to the operating room for biliary injury, intra-abdominal sepsis, and colonic anastomotic leak, while non from the

Table 1

Prior pelvic operations performed by gynecology prior to definitive hyperthermic intraperitoneal chemotherapy and cytoreductive surgery for appendiceal mucinous tumors.

Prior pelvic operation	n (%)
Total abdominal hysterectomy, bilateral salpingo-oophorectomy with appendectomy/ileocecectomy	8 (44.4%)
Diagnostic laparoscopy with biopsy	3 (16.6%)
Total abdominal hysterectomy, bilateral salpingo-oophorectomy without appendectomy	1 (5.6%)
Bilateral salpingo-oophorectomy with appendectomy	1 (5.6%)
Bilateral salpingo-oophorectomy without appendectomy	1 (5.6%)
Pelvic mass excision	2 (11.1%)
Left salpingo-oophorectomy	2 (11.1%)

Table 2

Demographics of patients with appendiceal mucinous tumor undergoing index gynecologic operation versus index cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

Characteristic	All (n = 36)	Index Operation:CRS/HIPEC (n = 18)	Index Operation: Gynecology (n = 18)	p-value
Age, year, median (IQR)	58 (14.5), 36	56.5 (19), 18	58.5 (14), 18	0.84 ^b
Race, n (%)				
Asian	5 (13.89)	2 (11.11)	3 (16.67)	1.00
Black	1 (2.78)	1 (5.56)	0 (0.0)	
Hispanic	11 (30.56)	5 (27.78)	6 (33.33)	
White	19 (52.78)	10 (55.56)	9 (50)	
BMI, median (IQR)	26.30 (7.4), 18	26.54 (7.64), 18	26.15 (7.90), 18	0.19
Prior abdominal surgery, n (%)	23 (63.89)	14 (77.78)	9 (50)	0.08
PSS				
0	5 (13.89)	4 (22.22)	1 (5.56)	0.002 ^a
1	13 (36.11)	10 (55.56)	3 (16.67)	
2	14 (38.89)	3 (16.67)	11 (61.11)	
3	3 (8.33)	0 (0.00)	3 (16.67)	
PSS >1	17 (48.57)	3 (17.65)	14 (77.78)	0.0006
Comorbidities, n (%)	19 (52.78)	13 (72.22)	6 (33.33)	0.019
Hypertension	6 (16.67)	5 (27.78)	1 (5.56)	0.18 ^a
Hyperlipidemia	7 (19.44)	4 (22.22)	3 (16.67)	1.0 ^a
Former smoker	4 (11.11)	4 (22.2)	0 (0.0)	0.1 ^a
COPD	2 (5.56)	2 (11.11)	0 (0.0)	0.48 ^a
Ascites	12 (33.33)	3 (16.67)	9 (50)	0.034
Cerebrovascular accident	1 (2.78)	1 (5.56)	0 (0.0)	1.0 ^a
CEA, ng/mL, median (IQR)	4.76 (47.2) 24	2.45 (14.3) 12	27.5 (53.65) 12	0.17 ^b
CA-125, U/mL, median (IQR)	43 (83.75) 20	53 (105), 7	33 (81.5), 13	0.74 ^b
PCI, median (IQR)	20 (16), 35	9 (15), 17	20.5 (5), 18	0.04 ^b
PCI >20, n (%)	17 (48.57)	6 (35.29)	11 (61.11)	0.13
Diagnosis to chemo/OR, days, median (IQR)	89.5 (105), 36	79.5 (96), 18	112 (136), 18	0.7 ^b
Pre operative chemotherapy, n (%)	10 (27.78)	6 (33.33)	4 (22.22)	0.46
Postoperative chemotherapy, n (%)	14 (40)	9 (50)	5 (29.41)	0.2
Pathologic diagnosis				
Appendiceal adenocarcinoma	21 (58.33)	14 (77.78)	7 (38.89)	0.04
Mucinous appendiceal neoplasm	15 (41.67)	4 (22.22)	11 (61.11)	
Grade				
Low grade	32 (88.89)	14 (77.78)	18 (100)	0.10 ^a
High grade	4 (11.11)	4 (22.22)	0 (0.0)	
CC score				
0/1	32 (88.89)	16 (88.89)	16 (88.89)	1.0 ^a
2	4 (11.11)	2 (11.11)	2 (11.11)	

IQR = Interquartile range, BMI = body mass index, PSS = prior surgical score, COPD = chronic obstructive pulmonary disease, CEA = Carcinoembryonic antigen, CA = cancer antigen, PCI = peritoneal cancer index; OR = operating room, CC = completion of cytoreduction.

^a Indicate two-sided Fisher's exact test.

^b Wilcoxon two sample t-test exact p-value.

non-PPO returned to the OR (Table 3). Multivariable regression was used to control for PCI >20 and confirmed that gynecologic operation increased the risk of 30-day morbidity after definitive CRS/HIPEC (OR 11.6, p < 0.01).

3.3. Secondary clinical outcomes

The length of operation was not different between the two groups. The median estimated blood loss was significantly higher in the PPO group (1375 mL vs. 400 mL, p < 0.01) and accordingly as well as the median intraoperative packed red blood cell (PRBC) transfusion requirements (5.5 units vs. 1.5 units, p = 0.01). The PPO

group had longer total median LOS (18 days vs. 9 days, p < 0.01). There was no difference in ICU or ventilator days, transfusion requirements within the first 24 postoperative hours, or readmission within 30 days between the groups (Table 3). The median length of follow-up for the study population was 40.7 months with no difference between the two groups. Recurrence occurred in 26.7% of patients. There was no difference in recurrence or progression-free survival between the two groups. No deaths occurred within 30 days.

Table 3
Clinical outcomes of patients with appendiceal mucinous tumor undergoing index gynecologic operation versus index cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

Outcome	All (n = 30)	Index Operation: CRS/HIPEC (n = 14)	Index Operation: Gynecology (n = 16)	p-value
Length of operation, minutes, median (IQR)	419 (291.5)	365 (130)	545 (389)	0.16 ^b
EBL in operation, mL, median (IQR)	400 (1150)	100 (350)	650 (1650)	0.002 ^b
Intraoperative PRBC transfusion, units, median (IQR)	2 (4.5)	0 (2)	3 (6)	0.018 ^b
LOS, days, median (IQR)	9 (8)	8 (2)	11.50 (10)	0.017 ^b
ICU, days, median (IQR)	3 (2)	2 (2)	3 (3)	0.039 ^b
Ventilator, days, median (IQR)	1 (1)	1 (1)	1 (1)	0.12 ^b
Transfusion in first 24 h, units, median (IQR)	18 (50)	6 (33.33)	12 (66.67)	0.045
Readmission within 30 days, n (%)	8 (22.22)	2 (11.11)	6 (33.33)	0.23 ^a
Morbidity, n (%)	19 (52.78)	6 (33.33)	13 (72.33)	0.019
Unplanned return to OR	3 (8.33)	0 (0.0)	3 (16.67)	0.22 ^a
Intraabdominal abscess	6 (16.67)	1 (5.56)	5 (27.76)	0.18 ^a
Skin Infection	4 (11.11)	0 (0.0)	4 (22.22)	0.1 ^a
Pneumonia	3 (8.33)	0 (0.0)	3 (16.67)	0.23 ^a
Reintubation	2 (5.56)	0 (0.0)	2 (11.11)	0.48 ^a
Anastomotic leak	2 (5.56)	1 (5.56)	1 (5.56)	1.00 ^a
Ileus	11 (30.56)	4 (22.22)	7 (38.89)	0.47 ^a
Acute kidney injury	2 (5.56)	0 (0.0)	2 (11.11)	0.48 ^a
Wound dehiscence	2 (5.56)	0 (0.0)	1 (5.56)	1.00 ^a
Sepsis	6 (16.67)	1 (5.56)	5 (27.78)	0.18 ^a
Clostridium difficile infection	2 (5.56)	0 (0.0)	2 (11.11)	0.49 ^a
DVT/PE	1 (2.78)	0	1 (5.56)	1.00 ^a
Urinary tract infection	4 (11.11)	0 (0.0)	4 (22.22)	0.1 ^a
CDC grade complication, n (%)				
I-II	27 (75.0)	16 (89.0)	11 (61.1)	0.05
III-IV	9 (25.0)	2 (11.1)	7 (39.0)	
CCI, median (IQR)	4.35 (29.6)	0 (0)	25.25 (43.20)	0.0016 ^b
Length of follow up, days, median (IQR)	709.5 (1185.5)	572 (1093)	1150 (1594)	0.58**
Recurrence, n (%)	8 (22.22)	3 (16.67)	5 (27.78)	0.69*

^a Indicate two-sided Fisher’s exact test.

^b Wilcoxon two sample t-test exact p-value. IQR = Interquartile range, EBL = estimated blood loss, PRBC = packed red blood cells, LOS = length of stay, ICU = intensive care unit, OR = operating room, CDC = clavien dindo classification, CCI = comprehensive comorbidity index.

4. Discussion

This study is the first to analyze patients with appendiceal mucinous tumors who underwent an index gynecologic operation for presumed ovarian origin prior to definitive cytoreductive surgery and HIPEC and compare their outcomes to patients without prior gynecologic surgery. The results confirmed our hypothesis that despite less comorbidities, having a prior gynecologic operation substantially increased the risk of morbidity of definitive CRS/HIPEC with an OR of 9.1. Importantly, CDC grade III/IV complications occurred four times more often in patients undergoing CRS/HIPEC with a prior gynecologic operation. We found that patients with prior gynecologic operation had higher median PCI and increased blood loss during definitive CRS/HIPEC. Finally, after adjusting for age, race, BMI, and PCI, they had 6.2 days longer overall length of stay (p = 0.04).

The results of our study are in line with prior studies that have shown prior surgery, especially debulking, before CRS/HIPEC is associated with worse outcomes. Even with less comorbidities going into CRS/HIPEC (p = 0.02), those who had previous gynecologic procedures had more postoperative complications with similar CCI/CCI rates. The most likely explanation for this is that the prior operation distorts anatomic planes, creates new planes for cancer to disseminate within, creates adhesions and scar tissue, and ultimately, leads to delays in definitive care [7]. Spilotis et al. showed that prior debulking or inappropriate minimally invasive procedures before definitive treatment of appendiceal mucinous neoplasm with CRS/HIPEC increased morbidity and decreased overall survival. They theorized this was because prior intervention promoted uncontrollable intraabdominal tumor growth due to tumor cell entrapment. For example, prior hysterectomy not only makes pelvic dissection more difficult, but also the absence of the uterus can allow cancer cells to more easily collect on the anterior

surface of the rectum. Definitive CRS/HIPEC is therefore more difficult as reflected in our study by the increased intraoperative blood loss in patients undergoing CRS/HIPEC after gynecologic operations. Similarly, Chua et al. found that patients with pseudomyxoma peritonei (PMP) who had undergone a prior debulking surgery required more blood transfusions during surgery and had longer operative times during definitive CRS/HIPEC [11].

Another issue contributing to our findings is that patients with index gynecologic operation may have longer time interval from symptom presentation to definitive treatment with CRS/HIPEC. This likely causes the increased tumor burden seen in this study from median PCI from 9 to 20.5 and possibly the increased presence of ascites [12]. Increased PCI leads to a more demanding cytoreduction with increased risk for adverse events. While our study showed that patients who underwent gynecologic operation tended to have a longer interval (>1 month) between tissue diagnosis to definitive treatment, this was not a statistically significant, and was likely a reflection of the small sample size.

Recognition of increased postoperative morbidity in patients with mucinous appendiceal neoplasms and prior gynecologic operations is crucial, as prior studies have shown that increased postoperative complications independently predict cancer-related survival. Choudry et al. showed that CDC grades 1 and 2 after CRS/HIPEC had a 40% increased risk of death, while CDC grades 3 and 4 had a 60% increased risk of death [13]. Schneider et al. similarly found that major complication (CDC IIIB and above) after CRS/HIPEC had a nearly five times higher risk for death due to cancer progression. They theorized this was due to an immunosuppressive state promoted by postoperative complications, which may block effective elimination of remaining peritoneal tumor cells by natural killer and cytotoxic T cells leading to increased tumor cell dissemination [14].

Moreover, prior surgery itself can lead to worse oncologic

outcomes after CRS/HIPEC. Milovanov et al. reported that extensive prior surgery prior to CRS/HIPEC for appendiceal cancer was associated with decreased overall survival (43% vs. 65% at 1 year and 26% vs. 54% at 3 years) [8]. Additionally, Sugarbaker et al. showed that PSS>2 in patients with appendiceal malignancy was associated with a 20% decreased overall survival [15]. One potential reason for this is that mucin-producing epithelial cells lack adhesive properties, which is why tumor deposits are found throughout the abdomen and not near the primary tumor, as is typical for high-grade cancers. Prior surgical wound sites, such as port sites, intestinal adhesions, and vaginal cuffs, provide a fibrin matrix to overcome the lack of adhesive properties of the tumor cells [16]. Zoetmulder et al. found that in patients with PMP that had a recurrence after CRS/HIPEC, 52% had recurrence in surgical scars and 60% at prior suture lines [17]. This highlights the importance of avoiding unnecessary dissection if an appendiceal tumor is found during a gynecologic procedure.

Over half of our patients underwent initial gynecologic operation for presumed ovarian malignancy, which is similar to prior studies. Dietrich et al. studied patients with appendiceal cancer and found that 62% of patients underwent initial surgery by gynecologic oncology [18]. Similarly, Chen et al. noted that 40% of appendiceal neoplasms were initially misdiagnosed as adnexal mass [19]. This likely occurs because 50–70% of patients with appendiceal neoplasm present with pelvic or adnexal mass [18,20]. Patients with pelvic masses are therefore presumed to be ovarian and referred to gynecologic oncology. GI malignancy as a potential cause is often forgotten due to rarity of disease, variable symptom presentation, and non-specific imaging characteristics [6]. Increased awareness of this misdiagnosis is needed throughout the medical community.

Patients with pelvic mucinous tumors of undetermined origin, especially those whose CA-125 levels are not suggestive of ovarian neoplasm, should be further worked up before being taken to the operating room for the wrong diagnosis. Wagner et al. recommends routine measurement of CEA, CA 19–9, and CA-125 in all patients with possibility of appendiceal neoplasm, as appendiceal neoplasms can also cause an elevated CA-125 [21]. Moreover, a CA-125/CEA ratio can be helpful preoperatively, as Sorensen et al. was able to use a ratio of <100 to identify patients with undiagnosed pelvic tumors that had non-ovarian malignancies with a specificity of 85% as appendiceal neoplasms can also cause an elevated CA-125 [22]. Additionally, some reports have suggested specific ultrasonographic markers of appendiceal neoplasms that could be of benefit if the exam is performed by a well-trained and experienced ultrasonographer [23–25]. Pelvic magnetic resonance imaging (MRI) has also been suggested to be more sensitive than CT in differentiation between ovarian and appendiceal tumors in some reports [26,27]. Colonoscopy should also be considered, as small case series were able to differentiate GI from ovarian tumors on the basis of endoscopic findings such as mucin escaping the appendiceal orifice [28,29]. Lastly, diagnostic laparoscopy can be offered if extensive preoperative work up is still unable to provide diagnosis [30]. However, this should be reserved as a last resort option, as it is only helpful if the appendix can be visualized and removed for a tissue diagnosis. Therefore, CRS/HIPEC should only be performed after a thorough multidisciplinary discussion and evaluation.

Limitations to this study include those inherent to a retrospective chart review, including missing data and non-systematic reporting. Additionally, a limited follow-up period prohibited evaluation of mortality and progression-free survival. Lack of power from small sample size may have contributed to the lack of statistically significant differences such as longer days from diagnosis to definitive CRS/HIPEC, longer length of operation of definitive CRS/HIPEC, and increased rates of recurrence of cancer in the

PPO group. Future studies are needed to study patients with appendiceal mucinous neoplasm and index gynecologic operations, as our study illustrated that this is a common occurrence with potentially serious implications.

5. Conclusion

Women with appendiceal mucinous tumors undergoing index gynecologic operation have a significantly higher morbidity compared to patients undergoing index CRS/HIPEC. Patients undergoing surgery for pelvic mucinous tumor of presumed gynecologic origin need to be counseled on the possibility of appendiceal neoplasm as a diagnosis and ideally evaluated by a multidisciplinary team prior to surgery. We recommend routine inclusion of CEA, Ca 19–9, CA-125, and colonoscopy in addition to imaging in the work-up of a pelvic mass. Most importantly, if there is suspicion for appendiceal mucinous tumor intraoperatively during a gynecologic operation, the surgeon should obtain tissue for diagnosis, but no further dissection and/or removal of female organs should be performed and the patient should be subsequently referred to a high volume center for treatment.

Disclosure

Alessio Pigazzi is a consultant for MedTronic and Ethicon. Jafari is consultant for Storz. No other conflicts of interest to disclose.

Declaration of competing interest

Alessio Pigazzi is a consultant for MedTronic and Ethicon. Jafari is consultant for Storz. No other conflicts of interest to disclose.

References

- [1] Gehrig PA, Boggess JF, Ollila DW, Groben PA, Van Le L. Appendix cancer mimicking ovarian cancer. *Nov-Dec Int J Gynecol Canc : official journal of the International Gynecological Cancer Society* 2002;12(6):768–72.
- [2] McBroom JW, Parker MF, Krivak TC, Rose GS, Crothers B. Primary appendiceal malignancy mimicking advanced stage ovarian carcinoma: a case series. *Sep Gynecol Oncol* 2000;78(3 Pt 1):388–90.
- [3] Sehoul J, Kopetsch OJ, Ricke J, et al. Primary mucinous adenocarcinoma of the appendix: a rare entity in the differential diagnosis of ovarian cancer. *Oct J Obstet Gynaecol Res* 2000;26(5):333–9.
- [4] Rouzbahman M, Chetty R. Mucinous tumours of appendix and ovary: an overview and evaluation of current practice. *J. Clin. Pathol.* 2014;67(3):193–7.
- [5] Tsai HW, Chen YJ, Twu NF, et al. Primary appendiceal malignancy mimicking advanced stage ovarian cancer. *Sep Taiwan J Obstet Gynecol* 2007;46(3):304–7.
- [6] Cristian DA, Grama FA, Becheanu G, et al. Low-grade appendiceal mucinous neoplasm mimicking an adnexal mass. *Rom. J. Morphol. Embryol. Rev. Roum. Morphol. Embryol.* 2015;56(2 Suppl):837–42.
- [7] Spiliotis J, Efstathiou E, Halkia E, Vaxeavidou A, Datsis A, Sugarbaker P. The influence of tumor cell entrapment phenomenon on the natural history of Pseudomyxoma peritonei syndrome. *May Hepato-Gastroenterology* 2012;59(115):705–8.
- [8] Milovanov V, Sardi A, Aydin N, et al. Extensive surgical history prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is associated with poor survival outcomes in patients with peritoneal mucinous carcinomatosis of appendiceal origin. *Jul Eur J Surg Oncol : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2015;41(7):881–5.
- [9] Paul BK, Ihemelandu C, Sugarbaker PH. Prior surgical score: an analysis of the prognostic significance of an initial nondefinitive surgical intervention in patients with peritoneal carcinomatosis of a colorectal origin undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Mar Dis Colon Rectum* 2018;61(3):347–54.
- [10] Clavien PA, Vetter D, Staiger RD, et al. The comprehensive complication index (CCI(R)): added value and clinical perspectives 3 Years "down the line". *Jun Ann Surg* 2017;265(6):1045–50.
- [11] Chua TC, Liauw W, Zhao J, Morris DL. Upfront compared to delayed cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei is associated with considerably lower perioperative morbidity and recurrence rate. *Apr Ann Surg* 2011;253(4):769–73.
- [12] El Halabi H, MacDonald R, Studeman K, et al. Delay of cytoreductive surgery

- and heated intraperitoneal chemotherapy in patients with appendiceal neoplasm. *Jul Am Surg* 2012;78(7):745–8.
- [13] Choudry MHA, Shuai Y, Jones HL, et al. Postoperative complications independently predict cancer-related survival in peritoneal malignancies. *Dec Ann Surg Oncol* 2018;25(13):3950–9.
- [14] Schneider MA, Eshmuminov D, Lehmann K. Major postoperative complications are a risk factor for impaired survival after CRS/HIPEC. *Aug Ann Surg Oncol* 2017;24(8):2224–32.
- [15] Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Dec Ann Surg Oncol* 1999;6(8):727–31.
- [16] Sugarbaker PH. Observations concerning cancer spread within the peritoneal cavity and concepts supporting an ordered pathophysiology. *Canc Treat Res* 1996;82:79–100.
- [17] Zoetmulder FA, Sugarbaker PH. Patterns of failure following treatment of pseudomyxoma peritonei of appendiceal origin. Oxford, England *Eur J Canc* 1990;32a(10):1727–33. Sep. 1996.
- [18] Dietrich 3rd CS, Desimone CP, Modesitt SC, et al. Primary appendiceal cancer: gynecologic manifestations and treatment options. *Mar Gynecol Oncol* 2007;104(3):602–6.
- [19] Chen J, Zhu L, Wu B. [Appendiceal mucocele mimicking right adnexal mass: a report of 25 cases]. *Zhonghua Yixue Zazhi*. Jun 21 2011;91(23):1637-1639.
- [20] Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. *Aug Am J Surg Pathol* 2003;27(8):1089–103.
- [21] Wagner PL, Austin F, Sathaiyah M, et al. Significance of serum tumor marker levels in peritoneal carcinomatosis of appendiceal origin. *Feb Ann Surg Oncol* 2013;20(2):506–14.
- [22] Sorensen SS, Mosgaard BJ. Combination of cancer antigen 125 and carcinoembryonic antigen can improve ovarian cancer diagnosis. *Nov Dan Med Bull* 2011;58(11):A4331.
- [23] Caspi B, Cassif E, Auslender R, Herman A, Hagay Z, Appelman Z. The onion skin sign: a specific sonographic marker of appendiceal mucocele. *Jan J Ultrasound Med : official journal of the American Institute of Ultrasound in Medicine* 2004;23(1):117–21. : quiz 122-113.
- [24] Degani S, Shapiro I, Leibovitz Z, Ohel G. Sonographic appearance of appendiceal mucocele. *Jan Ultrasound Obstet Gynecol : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2002;19(1):99–101.
- [25] Virgilio BA, Pontrelli G, Trevisan P, Sacchi D, Bernardini T, Scioscia M. Incidental diagnosis on transvaginal ultrasound of appendiceal mucocele arising on low-grade appendiceal mucinous neoplasm. *Ultrasound Obstet. Gynecol. Off. J. Int. Soc. Ultrasound Obstet. Gynecol* Oct 24 2018;54(3):412–4.
- [26] Hutchinson C, Lyske J, Patel V, Low G. Mucinous neoplasm of the appendix as a mimic of cystic adnexal pathology. *Journal of clinical imaging science* 2018;8:32.
- [27] Leonards LM, Pahwa A, Patel MK, Petersen J, Nguyen MJ, Jude CM. Neoplasms of the appendix: pictorial review with clinical and pathologic correlation. *Jul-Aug37. Radiographics : a review publication of the Radiological Society of North America, Inc.*; 2017. p. 1059–83. 4.
- [28] Mehmood S, Khan MQ. Mucinous adenocarcinoma ovary: diagnostic dilemma and the usefulness OF colonoscopy. *J Ayub Med Coll Abbottabad : J Ayub Med Coll Abbottabad*. Apr-Jun 2015;27(2):280-283.
- [29] Wirtzfeld DA, Price LM, Duggan MA, Medicott SA, Sutherland FR. Mucinous cystadenoma of the appendix in a patient with systemic lupus erythematosus. *Nov-Dec Can. J. Gastroenterol.=J. Can. Genet.Gastroenterol.* 1998;12(8):573–6.
- [30] Bravo R, Jafari MD, Pigazzi A. The utility of diagnostic laparoscopy in patients being evaluated for cytoreductive surgery and hyperthermic peritoneal chemotherapy. *Dec Am J Clin Oncol* 2018;41(12):1231–4.