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ORIGINAL ARTICLE

Risk factors for loss of bone mineral density after curative esophagectomy

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Abstract

Summary Micronutrient and fat malabsorption and altered enteroendocrine signaling occur after esophagectomy for cancer; however, the impact of malnutrition on bone health in this cohort has not been previously investigated. In this study, the prevalence of osteoporosis increased after curative surgery, associated with disease-specific, treatment-related, and population risk factors.

Purpose Improved oncologic outcomes in esophageal cancer (EC) have resulted in increased survivorship and a focus on long-term quality of life. Malnutrition and micronutrient malabsorption are common among patients with EC, but the effect on bone metabolism is not known. The aim of this study was to characterize changes in bone mineral density (BMD) following curative esophagectomy.

Methods Consecutive disease-free patients who underwent esophagectomy with gastric conduit for pathologically node-negative disease from 2000 to 2014 were included. BMD was assessed at vertebral levels T12-L5 by computed tomography using a simple trabecular region-of-interest attenuation technique, and serum markers of nutritional status and bone metabolism were examined. Independent risk factors for osteoporosis were identified by multivariable logistic regression.

Results Seventy-five consecutive patients were studied. Osteoporosis was present in 25% at diagnosis. BMD declined at 1 and 2 years postoperatively (144.3 ± 45.8 versus 128.6 ± 46.2 and 122.7 ± 43.5 Hounsfield Units (HU), $P < 0.0001$), with increased osteoporosis prevalence to 38% and 44% ($P = 0.049$), respectively. No significant postoperative change in vitamin D, calcium, or phosphate was observed, but alkaline phosphatase increased significantly ($P < 0.001$). While female sex ($P = 0.004$) and ASA grade ($P = 0.043$) were independently associated with osteoporosis at diagnosis, age ($P = 0.050$), female sex ($P = 0.023$), smoking ($P = 0.024$), and pathologic T stage ($P = 0.023$) were independently predictive of osteoporosis at 1 year postoperatively.

Conclusions Osteoporosis is prevalent among disease-free patients post-esophagectomy for EC, associated with disease-specific, treatment-related, and population risk factors. Strategies which minimize BMD decline should be considered to avoid fragility fractures in this cohort.

Keywords Bone · Bone mineral density · Esophagectomy · Esophageal cancer · Malnutrition · Malabsorption

Introduction

Advances in multimodal protocols and perioperative management, as well as increased early detection, have resulted in improved survivorship among patients with esophageal cancer treated with curative intent [1–3]. The recent CROSS randomized controlled trial established new benchmark oncologic outcomes in the multimodal treatment of esophageal cancer, attaining 47% 5-year survival among patients with locally advanced disease treated with neoadjuvant chemoradiotherapy and surgery [3]. With improving oncologic results, there is now an increasing focus on qualitative outcomes, and on the

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various issues impacting long-term quality of life in survivorship [4, 5].

Micronutrient malnutrition and weight loss are common among patients with esophageal cancer, and significantly impact quality of life [6–8]. Longitudinal studies indicate that 30–40% of disease-free patients experience > 15% weight loss at 3 years postoperatively [8, 9]. Our recent data demonstrate significant postoperative weight loss [10–13], loss of fat and lean body mass, and increasing prevalence of sarcopenia, even among those remaining disease-free in the long-term [14]. While dysphagia may affect a subset of patients in the early postoperative phase [15], reduced appetite, early satiety, and post-prandial symptoms appear to be major determinants of long-term postoperative nutritional status [7, 10, 11]. It is now additionally acknowledged that pancreatic exocrine insufficiency and small intestinal bacterial overgrowth may lead to fecal micronutrient loss, contributing to malnutrition among patients after esophagectomy [9, 16].

Despite myriad issues contributing to postoperative nutritional insufficiency after esophagectomy, few studies have investigated the long-term physiologic and functional consequences of chronic micronutrient malabsorption and malnutrition in this cohort. After other upper gastrointestinal operations such as total gastrectomy (TG) and Roux-en-Y gastric bypass (RYGB) for morbid obesity, analogous syndromes of bone mineral density (BMD) loss are described, with reductions in total, cortical, and trabecular bone and increased fracture risk after surgery [17–20]. Evidence of bone resorption is also reported following vertical sleeve gastrectomy (VSG) [21], which bears significant functional anatomic similarity to esophagectomy with gastric conduit reconstruction in terms of its impact on gastric volume, pressure, and rate of nutrient transfer to the small intestine [22, 23]. While skeletal unloading as a consequence of weight loss may contribute to reductions in BMD after bariatric surgery, the lack of such an effect following weight loss achieved through laparoscopic adjustable gastric banding (LAGB) suggests that altered gut physiology may play an important role in the decline of BMD observed after RYGB, TG, and VSG [20, 24, 25].

Common physiologic changes, exaggerated post-prandial gut hormone signaling, and altered nutrient transit, occurring across upper gastrointestinal surgeries, suggest that patients after esophagectomy may too be at risk of postoperative bone disease [10, 13]. However, the impact of esophagectomy on BMD and fracture risk has heretofore not been quantified.

The aim of this study was to characterize changes in BMD as determined by computed tomography (CT), among disease-free patients after esophagectomy for esophageal cancer, and to identify clinicopathologic characteristics independently associated with risk of postoperative BMD decline.

Methods

Study participants and data collection

The Esophageal and Gastric Centre at St. James's Hospital, Dublin, is a high-volume National Centre, and a database containing detailed clinical, demographic, staging, treatment, pathologic, and follow-up information is prospectively maintained for all patients with a diagnosis of esophageal cancer. Patients undergoing R0 radical esophagectomy with gastric conduit reconstruction for pathologically node-negative disease between 2000 and 2014 were retrospectively assessed for inclusion. Patients were included only if both an initial staging and 1 year postoperative CT of thorax, abdomen, and pelvis were conducted at our center and were available for review, and the patient remained disease-free at most recent follow-up. Changes in BMD and nutritional parameters among patients treated with neoadjuvant therapy and surgery were compared with those treated with surgery alone. Furthermore, to isolate the impact of esophageal cancer and its treatment with respect to BMD, an age- and sex-matched control cohort of patients ($n = 20$) who underwent CT on two occasions approximately 1 year apart for recurrent uncomplicated acute diverticulitis were also studied.

Patients who had a history of previous upper gastrointestinal resection, other malignancy, eating disorder, inflammatory bowel disease, chronic kidney disease, or other significant illness that might alter bone metabolism were excluded from analysis. The study was approved by the Hospital Review Board.

Treatment

Chemoradiotherapy and surgery

During this period, patients with locally advanced adenocarcinoma were treated with either pre and postoperative chemotherapy as per the MAGIC regimen [Etoposide, Cisplatin, Fluorouracil, or Capecitabine] [26] or neoadjuvant chemoradiation (either Cisplatin/5-Fluorouracil, 40 Gy/15 Fr or Carboplatin/Paclitaxel, 41.4 Gy/23 Fr) [27–29], while those with locally advanced squamous cell carcinoma were treated with chemoradiotherapy prior to surgery, as described above. Patients were scheduled to undergo surgical resection approximately 6 weeks after completion of neoadjuvant therapy. Reconstruction using a posterior mediastinal gastric conduit approximately 5 cm in width with hand-sewn anastomosis, and pyloroplasty, was performed as routine [10, 30].

Nutritional support

All patients underwent detailed dietetic assessment at a multidisciplinary clinic prior to surgery. A feeding jejunostomy was routinely placed at the time of resection and feed commenced on the first postoperative day. Oral intake was reintroduced from postoperative days 4 or 5. Once normal diet was achieved, the need for ongoing supplemental enteral feeding was reassessed in the outpatient dietetics clinic. Patients' nutritional status was then assessed at 3, 6, 12, and 18 months post-operatively, or more frequently if clinically indicated. Vitamin D levels were routinely assessed postoperatively and oral vitamin D supplementation commenced if insufficiency (30–50 nmol/L) or deficiency (< 30 nmol/L) was identified. Proton pump inhibitors were prescribed postoperatively for the prevention of late anastomotic stricture [31, 32].

Study design and protocol

This was a longitudinal study of thoracolumbar vertebral BMD as measured by CT, before and after curative esophagectomy. Two investigators reviewed all scans, and BMD at vertebral levels T12–L5 was assessed using the method described by Pickhardt et al. on a standard PACS Workstation (Siemens Healthcare, Erlangen, Germany) [33, 34]. Briefly, a single oval click-and-drag region of interest (ROI) was placed over anterior vertebral body trabecular bone, avoiding areas that would distort BMD readings, such as focal heterogeneity or lesions (Fig. 1). Mean CT attenuation for each ROI was recorded in Hounsfield Units (HU), a measure of radiodensity, similar to that used to generate BMD measurements using dual X-ray absorptiometry (DXA), which represents a linear transformation of the attenuation coefficient, such that distilled water at standard pressure and temperature has a radiodensity of 0 HU while air measures at − 1000 HU. For the purpose of this study, osteoporosis was defined using an L1 attenuation threshold of ≤ 110 HU, which was > 90% specific for distinguishing osteoporosis from osteopenia and normal BMD in previous studies [34].

This ROI method compares favorably to the more laborious phantomless quantitative CT as regards accuracy, with minimal interobserver variability on Bland-Altman plots, and requires no specialized equipment or software requirements [33, 34]. The accuracy of this method for estimation of BMD is unaffected by the use of intravenous contrast and no significant variability is observed in association with changes in diagnostic technology or imaging procedures [34].

The presence of vertebral compression fractures was assessed using the Genant visual semiquantitative method. Only obvious moderate or severe compression deformities were recorded, to minimize ambiguity as regards more subtle compression deformities. Serum markers of nutritional status and bone turnover were reviewed at each time-point.

Statistical analysis

Data were analyzed using GraphPad Prism (version 6.0) for Windows, GraphPad software (San Diego, CA, USA), and SPSS® (version 23.0) software (SPSS, Chicago, IL, USA). Univariable comparisons between groups were performed using the Student's *t* or Mann-Whitney *U* tests for continuous variables or χ^2 or Fisher's exact test for categorical variables. Paired Student's *t* or Wilcoxon signed rank tests were used to analyze changes in CT-BMD between diagnosis and 1 year. One-way repeated measures analysis of variance (ANOVA) with post hoc Holm-Sidak's test was used to analyze changes in continuous variables from diagnosis over multiple time-points. For the multivariable analysis, all clinically relevant variables were inputted into a multivariable logistic regression model using a forward stepwise selection procedure to assess their impact on osteoporosis risk. Data are reported as mean ± standard deviation unless otherwise specified. All statistical analyses were two-tailed with the threshold of significance set at $P < 0.05$.

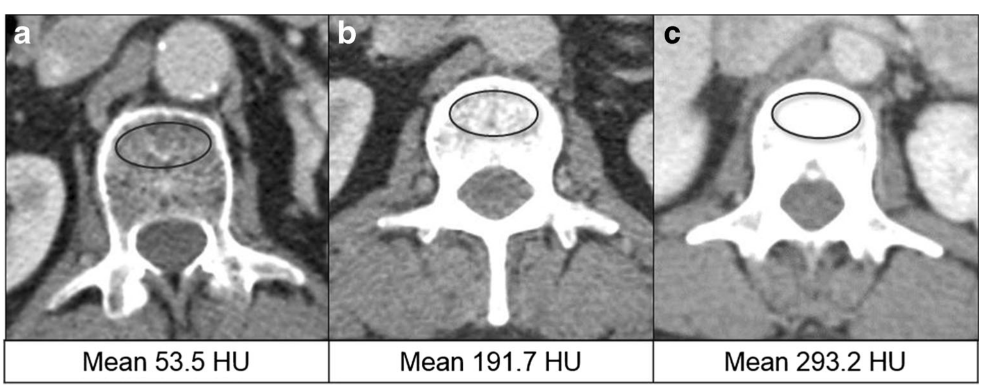

Fig. 1 Assessment of bone mineral density at the L1 vertebra. A single oval click-and-drag region of interest (ROI) was placed over anterior vertebral body trabecular bone, avoiding areas that would distort BMD readings, such as focal heterogeneity or lesions, and mean CT attenuation for each ROI was recorded in Hounsfield Units (HU)

Results

Patient characteristics

Seventy-five disease-free patients with a median follow-up of 43.4 months were studied (Table 1). Median age was 61 years (range 38–85) and patients had either early stage disease (n = 40 [53.3%]) or locally advanced disease which responded well to neoadjuvant therapy (n = 35 [46.7%]). Median American Society of Anaesthesiologists' (ASA) grade was 1 (range 1–3) and the majority of patients underwent 2-stage esophagectomy (2-stage, n = 38 [50.7%]; 3-stage, n = 17 [22.7%]; transhiatal, n = 20 [26.7%]). The predominant histologic type was adenocarcinoma (n = 57 [76.0%]).

Changes in CT-measured bone mineral density over time

At diagnosis, L1 BMD was 144.3 ± 45.8 HU and 19 patients (25%) were classified as osteoporotic (Supplementary

Table 1 Clinicopathologic characteristics of study population

	Entire population (n = 75)	Surgery only (n = 40)	Multimodal (n = 35)
Clinical characteristics			
Age, years, mean (SD)	60.6 ± 9.6	60.9 ± 10.7	60.2 ± 8.1
Sex, *N* (%)			
Female	17 (22.7)	8 (20.0)	9 (25.7)
Male	58 (77.3)	32 (80.0)	26 (74.3)
Smoking status at diagnosis, *N* (%)			
Ex-smoker	24 (32.0)	15 (37.5)	12 (34.3)
Current smoker	32 (42.7)	12 (30.0)	17 (48.6)
Never smoker	16 (21.3)	10 (25.0)	6 (17.1)
Unknown	3 (4.0)	3 (7.5)	–
BMI at diagnosis, kg/m^2, mean (SD)	27.0 ± 4.9	27.3 ± 4.7	26.6 ± 5.3
Weight at diagnosis, kg, mean (SD)	77.7 ± 17.3	79.1 ± 17.8	76.3 ± 16.9
ASA grade, mode (range)	1 (1–3)	2 (1–3)	1 (1–3)
Operation type			
2-stage	38 (50.7)	17 (42.5)	21 (60.0)
3-stage	16 (21.3)	5 (12.5)	11 (31.4)
Transhiatal	21 (28.0)	18 (45.0)	3 (8.6)
Postoperative LOS, median (range)	17 (9–53)	17 (11–53)	17 (9–32)
Pathologic characteristics			
Histologic type			
Adenocarcinoma	57 (76.0)	34 (85.0)	23 (65.7)
Squamous cell carcinoma	18 (24.0)	6 (15.0)	12 (34.3)
Clinical stage, *N* (%)			
T1	31 (41.3)	29 (72.5)	1 (2.9)
T2	13 (17.3)	9 (22.5)	6 (17.1)
T3	30 (40.0)	2 (5.0)	27 (77.1)
T4	1 (1.3)	–	1 (2.9)
N0	55 (73.3)	40 (100.0)	16 (45.7)
N1	13 (17.3)	–	12 (34.3)
N2	7 (9.3)	–	7 (20.0)
Pathologic stage, *N* (%)			
T0	14 (18.7)	–	10 (28.6)
T1	32 (42.7)	29 (72.5)	6 (17.1)
T2	16 (21.3)	9 (22.5)	8 (22.9)
T3	13 (17.3)	2 (5.0)	11 (31.4)
N0	75 (100.0)	40 (100.0)	35 (100.0)

SD standard deviation, *N* total number, *LOS* length of stay

Table 1). Patients with locally advanced disease requiring neo-adjuvant therapy (Table 1) were more likely to have osteoporosis at diagnosis (31% versus 10%, $P < 0.001$). For the population overall, BMD decreased significantly at 1 year post-operatively to 128.6 ± 46.2 HU ($P < 0.001$), and the incidence of osteoporosis was 13% (prevalence increased from 25 to 38%, $P = 0.049$, Fig. 2). BMD remained significantly reduced from diagnosis at 2 years postoperatively (122.7 ± 43.5 HU, $P < 0.001$) with a 19% incidence of osteoporosis (prevalence increased from 25 to 44%, $P = 0.01$ versus baseline). Cumulative incidence of any radiologic vertebral fracture at 2 years postoperatively was 3.5% and BMD among patients with any vertebral fracture was 61.8 ± 37.8 HU versus 130.5 ± 45.2 HU for those without ($P = 0.037$).

Among age- (57 [range 44–89] years, $P = 0.74$) and sex-matched (40% female, $P = 0.15$) unoperated control subjects, baseline prevalence of osteoporosis (20% vs 25%, $P = 0.99$) and BMD (149.1 ± 41.5 HU vs 144.3 ± 45.8 HU, $P = 0.69$) were similar to the esophagectomy group; however, no significant change in BMD was observed in the control group at 1 year (149.1 ± 41.5 HU vs 146.8 ± 36.2 HU, $P = 0.45$). In fact, control values remained remarkably stable on repeat assessment ($R^2 = 0.95$, $P < 0.0001$, Supplementary Fig. 1).

Biochemical nutritional and bone profile after esophagectomy

No significant change in corrected calcium, phosphate, or magnesium was observed between diagnosis and 1 year post-operatively (Table 2). Vitamins E and D also remained stable; however, vitamin A levels were lower at 1 ($P = 0.005$) and 2 years postoperatively ($P = 0.017$) compared with baseline, suggestive of possible fat malabsorption. Vitamin D levels pre-surgery were 49.1 ± 20.3 nmol/L with 21% and 34% of patients demonstrating vitamin D deficiency and insufficiency, respectively. The proportion of subjects classified as vitamin D deficient was 26% at 1 year and 11% at 2 years, while those classified as insufficient was 44% at 1 year and 42% at 2 years. Renal function did not significantly deteriorate at 1 year postoperatively, and significant reductions in urea

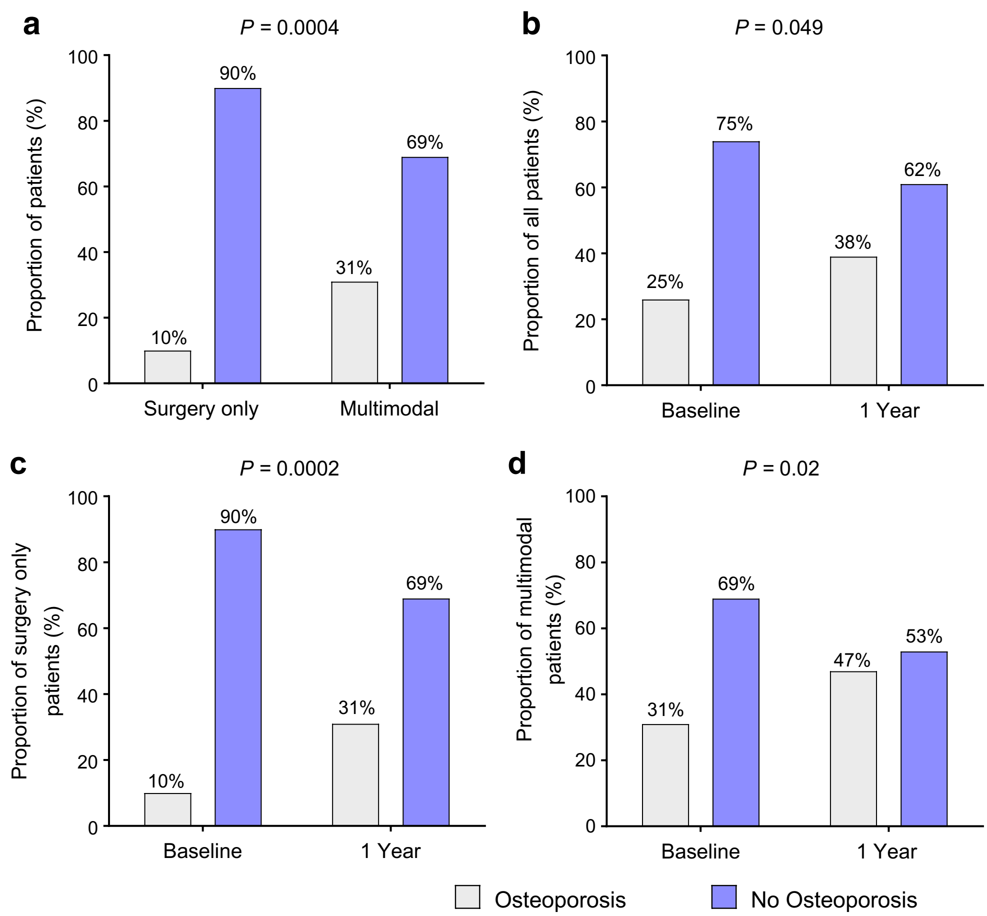

Fig. 2 Proportion of patients with CT evidence of osteoporosis pre- and post-esophagectomy. Significantly more patients in the multimodal cohort had CT evidence of osteoporosis at baseline, as compared with those who underwent surgery only (**a**, $P = 0.0004$). As shown in **b**, for the entire study population, the prevalence of osteoporosis increased significantly between diagnosis and 1 year postoperatively ($P = 0.049$). For the surgery only group, the prevalence of osteoporosis increased approximately two-fold from baseline to 1 year postoperatively (**c**, $P = 0.0002$), while in the multimodal cohort, the prevalence of osteoporosis also increased between baseline and 1 year (**d**, $P = 0.02$). χ^2 test

Table 2 Serum biochemical micronutrient profile

	Entire cohort ($n = 75$)			Surgery only ($n = 40$)			Multimodal ($n = 35$)		
	Baseline	1 Year	*P* value	Baseline	1 Year	*P* value	Baseline	1 Year	*P* value
Albumin, g/L	42.5 ± 3.3	41.5 ± 3.9	0.159	43.1 ± 3.1	41.6 ± 2.9	0.011	41.7 ± 3.4	41.5 ± 4.5	0.869
Calcium, mmol/L	2.33 ± 0.10	2.32 ± 0.10	0.223	2.32 ± 0.09	2.32 ± 0.09	0.600	2.35 ± 0.12	2.32 ± 0.11	0.403
Magnesium, mmol/L	0.82 ± 0.09	0.81 ± 0.06	0.602	0.82 ± 0.09	0.82 ± 0.04	0.782	0.84 ± 0.06	0.80 ± 0.08	0.180
Phosphate, mmol/L	1.04 ± 0.20	1.04 ± 0.17	0.625	1.05 ± 0.18	1.03 ± 0.16	0.661	1.03 ± 0.22	1.05 ± 0.18	0.796
Vitamin A, μmol/L	2.12 ± 0.58	1.64 ± 0.55	0.005	2.41 ± 0.70	1.59 ± 0.46	0.008	1.93 ± 0.39	1.68 ± 0.63	0.681
Vitamin D, nmol/L	49.1 ± 20.3	53.6 ± 28.6	0.490	49.6 ± 23.7	55.0 ± 24.9	0.581	49.0 ± 18.0	52.5 ± 32.1	0.340
Vitamin E, μmol/L	31.3 ± 6.2	29.5 ± 8.9	0.411	32.3 ± 7.0	31.3 ± 10.9	0.763	30.5 ± 5.7	28.1 ± 7.2	0.144
Urea, mmol/L	4.99 ± 1.68	4.92 ± 1.46	0.819	5.33 ± 1.29	4.78 ± 1.22	0.035	4.58 ± 1.99	5.0 ± 1.6	0.144
Creatinine, μmol/L	78.3 ± 15.9	71.3 ± 2.7	0.127	82.2 ± 15.6	71.7 ± 3.3	0.0007	73.9 ± 15.3	73.3 ± 3.6	0.439
Alkaline phosphatase, IU/L	81.1 ± 19.7	103.3 ± 34.3	<0.0001	82.3 ± 19.4	96.3 ± 33.2	0.006	79.8 ± 20.3	108.4 ± 34.7	<0.0001

Mean ± standard deviation, paired Student's *t* test or Wilcoxon signed rank test, as appropriate

IU international units

($P = 0.035$) and creatinine ($P < 0.001$) were observed among patients with early stage tumors, possibly reflecting reduced dietary protein intake and loss of skeletal muscle mass, respectively, from baseline. Of note, alkaline phosphatase levels increased significantly in both patient groups ($P < 0.01$) at 1 and 2 years postoperatively.

Factors associated with CT-measured bone mineral density

There was no relationship between alkaline phosphatase and BMD at diagnosis. At 1 year postoperatively, patients with osteoporosis demonstrated significantly greater serum alkaline phosphatase (114.5 ± 33.0 versus 95.5 ± 34.5 IU/L, $P = 0.044$) and phosphate levels (1.09 ± 0.14 versus 0.99 ± 0.14 mmol/L, $P = 0.04$), lower creatinine (65.3 ± 22.6 versus 78.4 ± 18.4 μmol/L, $P = 0.019$), and a trend towards lower albumin levels (40.5 ± 4.8 versus 42.4 ± 2.7 g/L, $P = 0.071$) compared with those without osteoporosis. Negative associations between both age and serum alkaline phosphatase and BMD at 1 year were observed, while a positive association with serum creatinine was seen, possibly reflective of skeletal muscle mass (Supplementary Fig. 2).

On multivariable analysis (Table 3), female sex (OR 8.95 [95% CI 2.05–38.99], $P = 0.004$) and greater ASA grade ($P = 0.043$) were independently associated with increasing risk of osteoporosis at diagnosis, while a trend suggestive of a relationship with baseline dysphagia ($P = 0.07$) was also observed. One year postoperatively, female sex (OR 5.20 [95% CI 1.25–21.66], $P = 0.023$), history of smoking (OR 7.76 [95% CI 1.31–45.90], $P = 0.024$), age at diagnosis (OR 1.07 [95% CI 0.99–1.15], $P = 0.05$), and pathologic tumor stage (OR 5.77 [95% CI 1.27–26.11], $P = 0.023$) were independent predictors of osteoporosis among patients after curative esophagectomy.

Discussion

Total gastrectomy (TG), Roux-en-Y gastric bypass (RYGB), and vertical sleeve gastrectomy (VSG) are associated with increased bone resorption and postoperative loss of BMD; however, changes in BMD after esophagectomy have heretofore not been described.

Failure to appropriately assimilate dietary calcium is implicated as an important precipitating factor in reduced BMD after RYGB and VSG [17, 18, 35–39], with early weight loss-independent increases in circulating markers of bone turnover (alkaline phosphatase, c-terminal telopeptide, and procollagen type 1) observed, despite optimization of vitamin D status [20, 24, 35, 40, 41]. Decreases in fractional calcium absorption after RYGB are accompanied by diminished levels of small intestinal TRPV6, the key vitamin D inducible calcium uptake channel [40, 42]. Furthermore, increased luminal fat related to pancreatic exocrine insufficiency, and reduced luminal acidity, may predispose to calcium malabsorption, while post-prandial suppression of bone resorption may additionally be attenuated—an effect which may arise directly from reductions in post-prandial serum calcium, and altered gut hormones [9, 25, 36].

It is now evident that several phenomena implicated in BMD loss after other foregut surgeries are also observed among patients after esophagectomy with gastric conduit [9, 11, 16]. However, despite data demonstrating that BMD loss after TG is associated with increased rates of vertebral deformity and fracture during long-term follow-up [18], the effect

Table 3 Multivariable logistic regression analysis to determine independent risk factors for osteoporosis

	Diagnosis		1 year postoperatively	
	P value	Odds ratio (95% CI)[a]	*P* value	Odds ratio (95% CI)[a]
Baseline characteristics				
Age at diagnosis	0.33	–	0.053	1.07 (0.99–1.15)
Sex (female vs. male)	0.004	8.95 (2.05–38.99)	0.023	5.20 (1.25–21.66)
Weight at diagnosis	0.78	–	0.48	–
ASA grade	0.043		0.23	
Grade 2 vs. grade 1	0.02	5.25 (1.30–21.30)	0.18	–
Grade 3 vs. grade 1	0.097	13.09 (0.63–273.49)	0.39	
Ever smoker	0.48	–	0.024	7.76 (1.31–45.90)
Dysphagia at diagnosis	0.071	–	0.612	–
Histologic type (SCC vs. ADC)	0.92	–	0.56	–
Clinical stage	0.106	–	0.45	–
Treatment factors[b]				
Neoadjuvant therapy	–		0.93	–
Operation type			0.77	
2-stage vs. transhiatal	–		0.87	–
3-stage vs. transhiatal			0.50	
Pathologic T stage (T0–2 vs. T3)	–		0.023	5.77 (1.27–26.11)
Postoperative LOS	–		0.64	–

CI confidence interval, *ASA* American Society of Anaesthesiologists, *SCC* squamous cell carcinoma, *ADC* adenocarcinoma, *LOS* length of stay

[a] Variables were inputted into a multivariable logistic regression model using a forward stepwise selection procedure

[b] For the prediction of baseline osteoporosis, only baseline characteristics were inputted

of esophagectomy on BMD and fracture risk is not known and, as such, evidence to direct primary prevention of osteoporotic fractures in this cohort is limited.

From the present study, where thoracolumbar vertebral BMD was longitudinally assessed by serial CT among pathologically node negative, long-term disease-free patients after esophagectomy, using a validated and reproducible method, a number of key observations can be made. Firstly, while population risk factors such as age, female sex, and smoking increased risk of osteoporosis in this cohort, patients after esophagectomy also experience a specific postoperative decline in BMD, in association with increased markers of bone turnover and without vitamin D deficiency. These data suggest that mechanisms underlying the observed specific decline in BMD after esophagectomy may be similar to those described among patients after TG and RYGB [18, 24, 35, 43].

Although the denervated gastric conduit may retain or recover a degree of acid secretory function [31], gastric acidity is consistently reduced [44, 45]. Reduced luminal acidity may contribute to impaired calcium absorption after esophagectomy, particularly in the context of ongoing proton pump inhibition, and as such calcium citrate supplementation may be more effective than the more widely used calcium carbonate [46, 47]. Muschitz et al. recently reported results of a randomized controlled trial assessing the impact of a targeted postoperative rehabilitation protocol on BMD decline among patients after RYGB and VSG. In this study, the intervention group (receiving oral vitamin D, calcium citrate, and protein supplementation, with prescribed physical exercise) exhibited attenuated BMD decline and markers of bone resorption compared with those receiving standard postoperative care [47]. These data highlight the potential for targeted interventions to effectively modify BMD loss among patients after foregut surgery. Future studies might aim to identify key drivers of the observed intervention effect, the value of pharmacotherapy such as bisphosphonates, required treatment duration, and impact on long-term fracture risk.

Fat malabsorption related to pancreatic exocrine insufficiency may additionally mediate calcium malabsorption through intraluminal saponification leading to BMD decline among patients after esophagectomy [9, 20, 46]. We have recently described outcomes following pancreatic exocrine replacement therapy (PERT) among patients screening positive for malabsorption using the modified gastrointestinal symptoms rating scale and fecal elastase-1 assessment [9, 48]. The role of PERT in the prevention of postoperative BMD loss among patients after esophagectomy requires further study; however, fecal elastase-1 inversely correlates with

BMD among patients with chronic pancreatitis, while PERT may improve BMD among other cohorts with pancreatic exocrine insufficiency [49, 50].

Furthermore, pathologic tumor stage was an independent predictor of osteoporosis at 1 year postoperatively, while dysphagia trended towards association with poor BMD at diagnosis. These data suggest that impaired preoperative intake may acutely impact BMD among patients with esophageal cancer, highlighting the importance of preoperative nutritional support in the patient with dysphagia.

A number of limitations are acknowledged—firstly, the highly specific attenuation threshold value used for the classification of osteoporosis may in fact underestimate the true prevalence of osteoporosis in the study population. As a screening tool, a threshold of 160 HU has previously yielded a sensitivity of 90%, with a specificity of 52%, may be more appropriate for initial identification of at-risk patients, and would have resulted in 76% of the study population being classified as osteoporotic at 1 year postoperatively. On the other hand, a balanced threshold of 135 HU would have resulted in a 1-year prevalence of 58% and has previously demonstrated sensitivity and specificity values of approximately 75% against DXA readings. Nonetheless, a linear association between vertebral attenuation and DXA T score is described, and as such, this highly specific threshold ensures that those with the most pronounced osteoporosis have been captured in the multivariable analysis [33, 34]. Furthermore, the previous study from Pickhardt et al. suggests that CT attenuation values may in fact be more accurate than DXA for prediction of vertebral compression fracture [34]. Rates of bisphosphonate use, calcium, and vitamin D supplementation were not routinely captured during the study period, nor were specific markers of bone turnover such as parathyroid hormone, c-terminal telopeptide, and bone-specific alkaline phosphatase. This notwithstanding, the highly significant increase in total serum alkaline phosphatase in correlation with BMD decline observed in this study is strongly suggestive of postoperative bone remodeling in this patient cohort. The extent to which bone remodeling after esophagectomy is related to postoperative body weight loss and resultant skeletal unloading, as compared with micronutrient deficiency or altered bone metabolism, requires further study. Lastly, the retrospective nature is acknowledged, while the strict inclusion criteria, encompassing only recurrence-free patients post R0 resection for pathologically node negative disease (in order to isolate the impact of esophageal cancer treatment with respect to BMD), limited the sample size. Future studies may prospectively characterize changes in BMD in long-term follow-up, determine associated fracture risk, and study risk factors for BMD loss in larger patient cohorts.

In conclusion, this study establishes for the first time that BMD decline occurs among long-term disease-free patients after esophagectomy. While population risk factors for osteoporosis apply to this cohort, these data also suggest that esophagectomy itself may increase osteoporosis risk. Clinical trials are needed to evaluate pharmacological interventions such as calcium citrate supplementation and bisphosphonates, as well as interventions which improve malnutrition relating to preoperative dysphagia, postoperative micronutrient malabsorption, and appetite impairment to attenuate loss of BMD and reduce fracture risk among long-term disease-free patients after esophagectomy.

Compliance with ethical standards

Conflicts of interest None.

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