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Clinical Significance of Frailty on Treatment Outcome in Nongeriatric Patients With Head and Neck Cancer and Esophageal Cancer Undergoing Curative-Intent Concurrent Chemoradiotherapy

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Abstract

Background: Whether the prevalence of frailty and its clinical significance are relevant to treatment outcomes in younger (aged < 65 years) cancer patients remains uncertain. This study aimed to evaluate the impact of frailty on treatment outcomes in younger cancer patients with head and neck and esophageal malignancy.

Material and methods: This multicenter prospective study recruited 502 patients with locally advanced head and neck and esophageal cancer during 2016–2017 in Taiwan, aged 20–64 years who received curative-intent concurrent chemoradiotherapy (CCRT) as first-line antitumor treatment. Baseline frailty assessment using geriatric assessment (GA) was performed for each patient within 7 days before CCRT initiation.

Results: Frailty was observed in 169 (33.7%) of 502 middle-aged patients. Frail patients had significantly higher incidences of chemotherapy incompletion (16.6% versus 3.3%, $P < .001$) and radiotherapy incompletion (16.6% versus 3.6%, $P < .001$) than fit patients. During CCRT, frail patients had a significantly higher percentage of hospitalizations (42.0% versus 24.6%, $P < .001$) and a trend toward a higher percentage of emergency room visits (37.9% versus 30.0%, $P = .08$) than fit patients. Frail patients more likely had a significantly higher incidence of grade ≥ 3 adverse events than fit patients during CCRT. The 1-year survival rate was 68.7% and 85.2% (hazard ratio 2.56, 95% confidence interval 1.80–3.63, $P < .001$) for frail and fit patients, respectively.

Conclusions: This study demonstrated the significance of pretreatment frailty on treatment tolerance, treatment-related toxicity, and survival outcome in younger patients with head and neck and esophageal cancer undergoing CCRT. While GA is

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commonly targeted toward the older population, frailty assessment by GA may also be utilized in younger patients for decision-making guidance and prognosis prediction.

Keywords
vulnerability, geriatric assessment, frailty, chemoradiotherapy

Introduction

Frailty is defined as an accumulative decline in physiological reserve, leading to multiple functional disabilities and vulnerability to subsequent morbidity and mortality.[1] Frailty is frequently reported to be associated with poor survival outcome,[2,3] higher treatment-related toxicity,[3,4] and poor tolerance to antitumor therapy in cancer patients.[3,4] Thus, frailty has often been used as an indicator for tailored therapy or predictors and prognosticators of antitumor treatment in oncologic practice.[5,6]

As the prevalence of frailty increases with age, several international guidelines routinely recommend frailty assessment for older (aged ≥ 65) oncologic patients before the initiation of antitumor treatments.[7–9] However, frailty occurs independent of chronological age and is frequently observed due to external stressors such as acute illness or high-intensity antitumor treatment.[10] While the identification of frailty has contributed to clinical decision-making among older oncologic patients, the prevalence of frailty and its clinical relevance to antitumor treatment outcomes in younger (age < 65) cancer patients remain uncertain.[11] Therefore, since the prognostic relevance of frailty in older patients with cancer has been substantial, the impact of frailty on younger patients with cancer has become an appealing issue.

Radical resection is the most effective curative treatment option for patients with head and neck cancer (HNC) and esophageal cancer (EC). For locally advanced disease which is difficult to achieve complete resection or intent to organ preserve, multimodal treatment with preoperative chemoradiotherapy or definitive concurrent chemoradiotherapy (CCRT) is one of the treatment modalities for patients with locally advanced HNC[12] and EC,[13] for which the majority of patients were diagnosed at the age of 40–60 years.[14] Owing to the high treatment intensity of CCRT, it inevitably leads to substantial treatment-related complications.[12,13] Therefore, it is important to identify vulnerable patients who are at the highest risk of adverse outcomes during high-intensity antitumor treatment.

As GA is a comprehensive measurement tool and has been widely used, we hypothesized that GA might be a reliable tool for assessing frailty in younger patients with cancer. This study aimed to assess frailty using GA and evaluate the impact of frailty on treatment outcomes among younger patients with HNC and EC undergoing curative-intent CCRT.

Materials and Methods

This is a secondary analysis of a multicenter prospective study investigated the effectiveness of frailty status in the prediction of treatment-related severe adverse events (sAEs), tolerance of antitumor therapy, and survival outcome among younger patients with cancer.[2]

Patient Selection

Assuming one-third of patients had frailty in our patient cohort, at least 477 patients were required to be enrolled to provide 80% power to detect a 1 year mortality difference of 10% for a dichotomous predictor in logistic regression. A total of 726 patients were consecutively assessed for eligibility between August 2016 and December 2017 from three medical institutes in Taiwan. The eligibility criteria were as follows: patients aged 20–64 years, those histologically proven with locally advanced HNC or EC, who were planning to receive as the first-line antitumor treatment, those with Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and those having acceptable bone marrow, liver, and renal function. Locally advanced disease was defined as T4 or nodal positive tumor of the nasopharynx, oropharynx, hypopharynx, or larynx, and any unresectable tumor of the oral cavity in HNC and ≥ T2 classification, or any regional node-positive tumor in EC. Patients with age ≥ 65 years ($n = 91$), reception of chemotherapy or radiotherapy alone due to ECOG > 2 or poor liver and renal reserve ($n = 68$), metastatic disease ($n = 49$), decline to participate ($n = 11$), and inability to complete the frailty questionnaire for any reason ($n = 5$) were excluded. Tumor staging was performed according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system in this study. All patients provided written informed consent before inclusion into the study. The study protocol was approved by the institutional review board (No.: 1608080002). Figure 1 shows the study flowchart.

Concurrent Chemoradiotherapy and Toxicity Recording

All patients with HNC received intensity-modulated or arc radiotherapy at a conventional fractionated daily dose of 200 cGy for 5 consecutive days per week, with a total

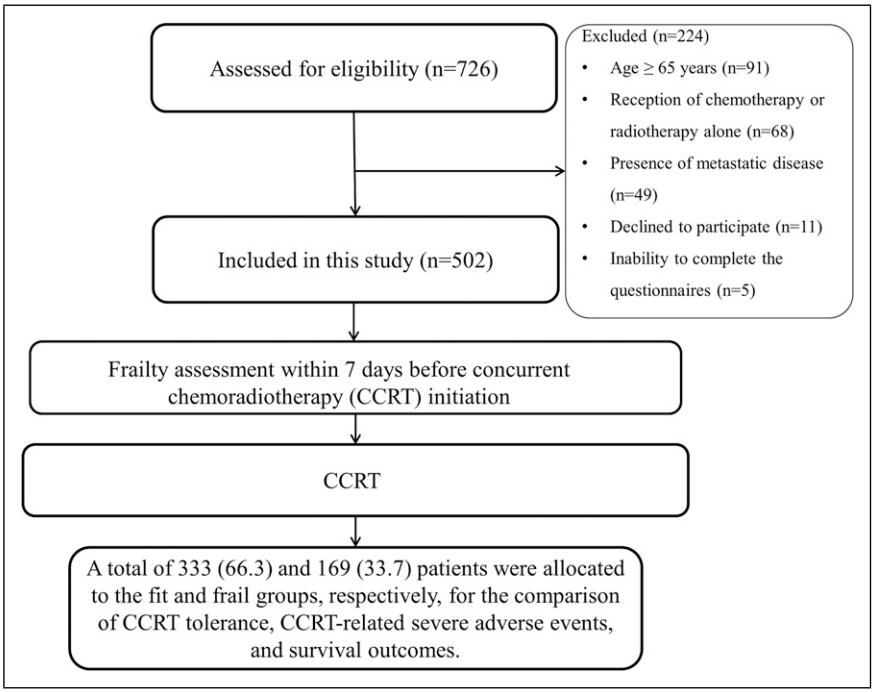

Figure 1. Flowchart of the study participant selection process.

prescribed radiotherapy dose of 7,000–7,400 cGy over 7 weeks; concurrently administered chemotherapy with either cisplatin (40 mg/m^2 every 1 week or 100 mg/m^2 every 3 weeks),[15] P60F regimen (cisplatin 60 mg/m^2 on day 1 plus continuous infusion of 5-fluorouracil 800 mg/m^2 on days 1–5, every 2 weeks),[16] or PUL regimen (cisplatin 50 mg/m^2 on day 1, Tegafur-uracil [TTY Biopharm Co Ltd, Taipei, Taiwan] 300 mg/m^2/day, and oral leucovorin 60 mg/day on days 1–14, every 2 weeks.[17] EC patients received radiotherapy at a dose of 180 cGy for 5 consecutive days per week, with a total prescribed radiotherapy dose of 4,140 cGy over 5 weeks; concurrently administered chemotherapy with either PC regimen (paclitaxel 50 mg/m^2 plus carboplatin area under the curve of 2 mg per milliliter per minute every week)[13] or P100F regimen (cisplatin 100 mg/m^2 on day 1 plus 5-fluorouracil 1000 mg/m^2 on days 1–4 every week)[18] concurrent with radiotherapy.

Treatment outcomes (toxicity, treatment tolerance, and survival outcome)

Concurrent chemoradiotherapy-related toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute, version 3. Any grade III or higher toxicity was defined as sAE. Complications of CCRT were defined as incomplete treatment, emergency room visits, or hospitalization due to any reason during the CCRT period. The patients' vital status and grades for any adverse event were evaluated at least weekly during CCRT treatment. All adverse events or treatment-related complications were recorded from CCRT initiation till 1 month after the end of CCRT. Patients who received less than 90% of the protocol specified the radiotherapy dose or the full course of chemotherapy due to any cause were considered to have incomplete radiotherapy or chemotherapy,[13–20] respectively.

All enrolled patients were followed up until May 31, 2019, or until death. Overall survival (OS) was calculated from the date of cancer diagnosis until the date of death from any cause and the last day of follow-up.

Frailty Assessment

Geriatric assessment was used as the baseline frailty assessment and performed within 7 days before CCRT initiation and included the following seven frail dimensions: functional status as assessed by activities of daily living[21]; instrumental activities of daily living[22]; nutritional status as assessed by mini-nutritional assessment short-form[23]; comorbidity as assessed by the Charlson comorbidity index[24]; polypharmacy as assessed by types of medications used[25]; mood as assessed by the Geriatric Depression Scale-4 questions[26]; and cognition,[27] mobility,[23] and social support as assessed by living with others or alone.[28] Frailty was defined as the presence of two or more frail conditions[3] in this study.

Statistical Analysis

Descriptive analyses were performed to summarize the patient and tumor characteristics. The Kruskal–Wallis test for continuous and ordinal variables and chi-square (or Fisher's exact

test) for categorical variables were used for in-group comparisons. Univariate and multivariate logistic regression analyses were performed to estimate the relative risk (RR), and 95% confidence interval (CI) for variables associated with complications of CCRT. Survival outcome was calculated according to the Kaplan–Meier method. Log-rank tests were used to determine significant differences between the survival curves. A Cox regression model was performed to estimate the hazard ratio for variables associated with overall survival. SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. All statistical assessments were two-sided, and a P-value < .05 was considered statistically significant.

Results

Patient Demographics

The basic characteristics of the 502 patients are shown in Table 1. The majority of the patients were male (89.2%), and the median age was 53 (range, 24–64) years. Half of the patients (52%) had excellent performance status with an ECOG score of 0, and 53.2% of the patients had stage IVa or IVb disease. The most common primary tumor site was the oropharynx (25.5%), followed by the esophagus (21.7%) and nasopharynx (19.7%). No significant differences were observed between the fit and frail groups in terms of sex, age, educational level, occupation, lifestyle habits with alcohol drinking, smoking or betel quid-chewing, tumor stage, and chemotherapeutic regimens. A higher proportion of fit patients were married (76.6% versus 63.3%, P = .002), had ECOG performance status 0 (61.9% versus 32.5%, P < .001), and had a greater number of tumors originating from the nasopharynx (25.5% versus 8.3%, P < .001) than that of frail patients.

Frailty Assessment Results

The assessment tool and cutoff standard for each frail dimension of the 502 patients are shown in Table 2. Malnutrition was the most common frail condition (55.2%), followed by polypharmacy (26.3%) and comorbidities (22.9%). The least common frail condition was cognition deficit (7.2%) and mobility/falls (1.4%).

The distribution of frail condition proportion is presented in Table 3. The median number of frailty dimensions was 1 (range 0–5). Accordingly, 333 (66.3%) and 169 (33.7%) patients were allocated to the fit and frail groups, respectively, depending on the CGA.

Tolerance of Concurrent Chemoradiotherapy

In total, 7.8% and 8.0% of the patients had incomplete chemotherapy and radiotherapy, respectively. Frail patients had significantly higher incidences of incomplete chemotherapy (16.6% versus 3.3%, P < .001) and incomplete radiotherapy (16.6% versus 3.6%, P < .001) than fit patients.

In total, 164 (32.7%) patients had emergency room visits and 153 (30.5%) patients needed hospitalization during the CCRT course. Frail patients had a significantly higher frequency of hospitalization (42.0% versus 24.6%, P < .001) and a trend toward a higher frequency of emergency room visits (37.9% versus 30.0%, P = .08) than fit patients.

Frail patients had a higher risk of incomplete chemotherapy (crude RR 5.81, 95% CI 2.82–12.0, P < .001), incomplete radiotherapy (crude RR 5.31, 95% CI 2.63–10.7, P < .001), hospitalization (crude RR 2.22, 95% CI 1.50–3.29, P < .001), and emergency room visits (crude RR 1.42, 95% CI .96–2.10, P = .08) **(**Supplementary Table 1**)**. Notably, frailty status maintained itself as an independent risk factor for incomplete chemotherapy (adjusted RR 4.29, 95% CI 1.99–9.24, P < .001), incomplete radiotherapy (adjusted RR 4.58, 95% CI 2.14–9.79, P < .001), and hospitalization (adjusted RR 1.83, 95% CI 1.20–2.80, P = .005) after adjusting for age, sex, cancer type, ECOG performance status, tumor stage, and chemotherapeutic regimen in the multivariate analysis.

Concurrent Chemoradiotherapy-Related Severe Adverse Events

All common sAEs with an incidence of ≥ 3% during CCRT are listed in Table 4.

Overall, 165 (32.5%) patients had any severe hematologic toxicity, and 355 (70.7%) patients had any severe non-hematologic toxicity after CCRT. Frail patients were more likely to have a significantly higher incidence of grade ≥ 3 leukopenia, hemoglobin, infection, hyponatremia, and hypokalemia than fit patients during CCRT.

Totally, three patients in the fit group (1 patient died of neutropenic fever and 2 patients died of pneumonia) and two patients in the frail group (1 patient died of neutropenic fever and 1 patient died of pneumonia) died during the course of CCRT. No statistical difference in incidence of grade 5 toxicity occurred between the two groups.

Survival Outcome

The median follow-up duration for surviving patients was 13.4 (range: 1.9–31.9) for all patients. Figure 2 shows the survival outcome based on frailty status. The 1-year and 2-year survival rates were 85.2% and 74.7% for fit patients and 68.7% and 45.8% for frail patients, respectively. Survival time was significantly poorer in frail patients than in fit patients (HR 2.56, 95% confidence interval 1.80–3.63, P < .001). Frail patients had a 1.84-fold increased hazard (95% confidence interval 1.28–2.66, P = .01) of mortality compared with that in fit patients after adjusting for age, sex, cancer type, ECOG performance status, tumor stage, and chemotherapeutic regimen in the multivariate analysis.

Table 1. Patients' basic characteristics (n = 502).

Variable	Category	Total cohort (n = 502), n (%)	Fit (n = 333), n (%)	Frail (n = 169), n (%)	P
Sex	Male	448 (89.2)	297 (89.2)	151 (89.3)	.99
	Female	54 (10.8)	36 (10.8)	18 (10.7)	
Age	Median (range)	53 (24–64)	52 (24–64)	53 (33-64)	.33
Marital status	Married	362 (72.1)	255 (76.6)	107 (63.3)	.002
	Others	140 (27.9)	78 (23.4)	62 (36.7)	
Education	Less than high school	69 (13.7)	45 (13.5)	24 (14.2)	.09
	High school graduate	318 (63.3)	202 (60.7)	116 (68.6)	
	Associate/bachelor's degree or higher	115 (22.9)	86 (25.8)	29 (17.2)	
Occupation	Yes	386 (76.9)	264 (79.3)	122 (72.2)	.14
	No	116 (23.1)	69 (20.7)	47 (27.8)	
Smoking	Yes	410 (81.7)	265 (79.6)	145 (85.8)	.11
	No	92 (18.3)	68 (20.4)	24 (14.2)	
Drinking	Yes	417 (83.1)	271 (81.4)	146 (86.4)	.17
	No	85 (16.9)	62 (18.6)	23 (13.6)	
Betel quid-chewing	Yes	337 (67.1)	223(67.0)	114 (67.5)	.99
	No	165 (32.9)	110 (23.0)	55 (32.5)	
ECOG performance	0	261 (52.0)	206 (61.9)	55 (32.5)	<.001
	1	230 (45.8)	127 (38.1)	103 (60.9)	
	2	11 (2.2)	0	11 (6.5)	
Cancer type	Nasopharynx	99 (19.7)	85 (25.5)	14 (8.3)	<.001
	Oropharynx	128 (25.5)	86 (25.8)	42 (24.9)	
	Oral cavity	72 (14.3)	39 (11.7)	33 (19.5)	
	Hypopharynx	94 (18.7)	69 (20.7)	25 (14.8)	
	Esophagus	109 (21.7)	54 (16.2)	55 (32.5)	
Tumor stage by AJCC	1	12 (2.4)	10 (3.0)	2 (1.2)	.60
	2	69 (13.7)	46 (13.8)	23 (13.6)	
	3	154 (30.7)	99 (29.7)	55 (32.5)	
	4a or 4b	267 (53.2)	178 (53.5)	89 (52.7)	
Chemotherapy regimen	Platinum monotherapy	109 (21.7)	67 (20.1)	42 (24.9)	.25
	Platinum combination	393 (78.3)	266 (79.9)	127 (75.1)	

Note: ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer.

Table 2. Pretreatment frailty outcomes by geriatric assessment (n = 502).

Frailty dimension	Measures	Number of items	Score range	Cutoff value	n (%)
Nutrition	MNA-SF[22]	6	0–14	≤11	277 (55.2)
Polypharmacy	Number of medications[24]	1	0–∞	≥5	132 (26.3)
Comorbidity	CCI[23]	17	0–33	≥2	115 (22.9)
Social support	Living alone[27]	1	0–1	1	63 (12.5)
Mood	GDS-4[25]	4	0–4	≥2	53 (10.6)
Functional status	Barthel index (ADL)[20]	10	0–100	<100	50 (10.0)
	Lawton scale (IADL)[21]	8	0–8	≤7	41 (8.2)
Cognition	Mini-Mental State Examination[26]	11	0–30	≤23	18 (7.2)
Mobility/falls	Number of falls[24]	1	0–∞	≥2	7 (1.4)

Note: MNA-SF, Mini-Nutritional Assessment-Short Form; CCI, Charlson comorbidity index; GDS, Geriatric Depression Scale; ADL, activities of daily living; IADL, instrumental activities of daily living.

A total of 127 patients died at the study end, the main causes of death are presented in Supplementary Table 2. The most common cause of death is progressive disease (63.8%), followed by pneumonia (16.7%), other sepsis (12.7%), and miscellanies (7.1%). No statistical intergroup difference was noted.

Table 3. Distribution of Geriatric Assessment Dimensional Impairment (n = 502).

No. of dimensional impairment	n (%)	Cumulative, n (%)
0	145 (28.9)	145 (28.9)
1	188 (37.5)	333 (66.3)
2	102 (20.3)	435 (86.7)
3	50 (10.0)	485 (96.6)
4	10 (2.0)	495 (98.6)
5	7 (1.4)	502 (100)

Discussion

This study prospectively explored the effect of frailty on tolerance, adverse events, and survival outcomes in younger patients with HNC and EC receiving curative-intent CCRT. According to GA, one-third of the study cohort presented frailty upon initiation of antitumor therapy. Furthermore, frailty was significantly associated with poor tolerance to CCRT, a higher percentage of hospitalization, and a higher incidence of treatment-related sAEs in younger patients with

Table 4. Severe Adverse Event of Concurrent Chemoradiotherapy According to Frailty Status.

	Total (n = 502)		Fit (n = 333)		Frail (n = 169)		
Severe adverse event	n	%	n	%	n	%	P
Any grade III hematological toxicity	165	32.9	85	25.5	80	47.3	<.001
Leukopenia	116	23.1	66	19.8	50	29.6	.018
Neutropenia	78	15.5	44	13.2	34	20.1	.051
Hemoglobin	75	14.9	32	9.6	43	25.4	<.001
Platelet	27	5.4	15	4.5	12	7.1	.29
Neutropenic fever	9 (2)	1.8 (.4)	4 (1)	1.2 (.3)	5 (1)	3.0 (.6)	.34
Any grade III non-hematological toxicity	355	70.7	238	71.5	117	69.2	.61
Mucositis	231	46.0	158	47.4	73	43.2	.39
Infection with normal neutrophil	95 (3)	18.9 (.6)	47 (2)	14.1 (.6)	48 (1)	28.4 (.6)	<.001
Hypertension	54	10.8	35	10.5	19	11.2	.88
Hyponatremia	52	10.4	20	6.0	32	18.9	<.001
Emesis	42	8.4	28	8.4	14	8.3	.99
Hypokalemia	33	6.6	12	3.6	21	12.4	<.001
Hyperglycemia	26	5.2	14	4.2	12	7.1	.20
AST or ALT elevation	14	2.8	10	3.0	4	2.4	.78

Note: AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Parentheses indicate the patients with grade 5 toxicity.

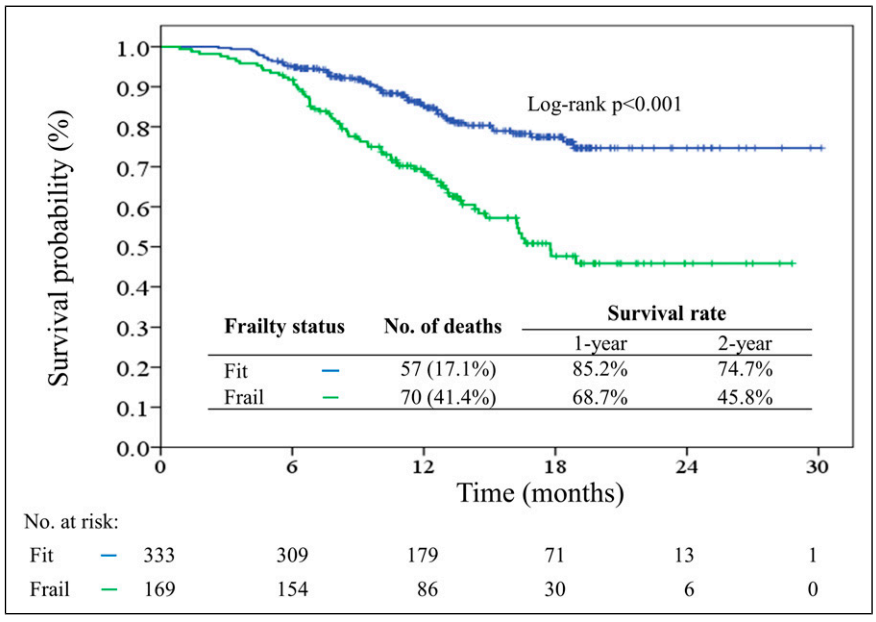

Figure 2. Survival outcome according to frailty status.

cancer. Finally, this study demonstrated that frailty was associated with a poor survival outcome in such patients compared with that in fit patients. Our study suggests that pretreatment frailty could serve as a predictor and a prognosticator for younger patients with HNC and EC undergoing curative-intent CCRT.

Two systemic reviews reported that geriatric conditions, including functional and cognitive impairment, depressive symptoms, and social isolation were highly prevalent in HNC and EC patients.[29,30] Half of the study cohorts had a mean age < 65 years in both reviews. Both reviews suggested that geriatric conditions were independent of chronological age and associated with adverse health outcomes.[29,30] However, in both reviews, parameters used to evaluate geriatric conditions such as functional status, social support, or mood, were not fully explored. Neither study was designed to report the impact of frailty in younger patients with HNC or EC. Geriatric assessment (GA), which includes multi-dimensional assessment, is the gold standard tool for frailty assessment in the older population.[31] Several international guidelines had been recommended routine GA evaluation of onco-geriatric patients before administering antitumor treatments. While frailty has been an established prognostic factor among the older population, frail assessment's prognostic significance may be investigated among younger HNC and EC patients as these patients' clinical conditions resemble geriatric conditions. However, there is no consensus regarding the tools used to identify frailty in the younger population.

Only a few published studies have addressed the prevalence and impact of frailty in younger patients.[32] In a healthy population, the prevalence of frailty was reported to be approximately 5.3–6.9% among those aged 18–64 years in a Canadian health measures survey using the frailty index.[33] By using the FRAIL scale, the prevalence of frailty was 7.4% among African Americans aged 49–65 years in the community setting.[34] As frailty is an accumulative decline in the physiological reserve, acute illness or its sequelae might further increase the penetration of frailty.[32] For example, up to 18.6% of young adult survivors of childhood leukemia were reported to be frail.[35] Adult survivors of allogeneic hematopoietic cell transplantation (HCT) with active graft-versus-host disease had a 15-fold higher risk of frailty than autologous HCT survivors.[36] Furthermore, frailty was present in approximately 28–33% of younger patients with critical illnesses in the intensive care unit setting.[37,38] Consistently, frailty was highly prevalent (33.7%) among younger patients with HNC and EC in our study. The prevalence of frailty was similar to that of older patients with HNC (37%),[39] suggesting that cancer diagnosis, regardless of age, significantly contributed to the frailty phenotype in patients with cancer. As frailty is highly prevalent in patients with cancer, routine frailty assessment might be necessary for all adult patients with cancer upon the initiation of antitumor treatment, regardless of their age.

Several studies have shown an association between frailty and negative outcomes in younger patients, for instance, frail patients were associated with higher morbidity and mortality in patients of any age undergoing head and neck surgery.[40] In patients with end-stage liver disease with a median age of 60 years, frailty status was significantly correlated with increased mortality after liver transplantation.[41] According to previous reports, our study showed that frailty was a negative predictor of treatment tolerance and sAE of CCRT as well as a poor prognostic factor for survival outcome in younger patients with cancer. The inferior survival outcome of frail patients might contribute to the inadequate treatment intensity owing to the higher treatment incompletion rate among frail patients. The higher incidence of treatment-related sAEs and hospitalization rate among frail patients might further interrupt the treatment schedule of CCRT. Our study highlighted the importance of enhancement in supportive care for frail patients during antitumor treatment to counterbalance the impact of treatment-related toxicity. To maximize the antitumor treatment effect and minimize treatment-related toxicity of CCRT, further study regarding tailored therapy for frail patients with HNC and EC is warranted.

While CCRT is the standard treatment for patients with locally advanced HNC and[40,42] more than 70% of these patients experience sAEs, and 6%–23% of patients need treatment interruption during the CCRT course.[43,44] In line with previous studies,[43,44] our study showed that 32.9% and 70.7% of the patients in the cohort experienced hematologic and non-hematologic AEs, respectively, and 7.8% and 8.0% of patients were unable to complete the planned chemotherapy and radiotherapy, respectively. Because a substantial number of patients are susceptible to CCRT-related sAEs, our study showed that pretreatment frailty assessment might offer an objective method to identify vulnerable patients and to predict treatment compliance.

Poor performance status is a well-known negative predictor of treatment intolerance and survival outcome in oncologic practice.[45] However, the performance scale neglects the effects of other physical conditions such as nutrition, comorbidity, mood, and social support, which are also well-known prognostic factors for patients with HNC and EC.[46] As compared to the performance scale, frailty assessment evaluates multiple dimensional abilities including physical activity, comorbidity, nutrition, cognition, and social support, which would be more reliable in identifying vulnerable patients with cancer receiving antitumor therapy. Regarding the functional defect of frailty domains, our patient cohort had the highest prevalence of malnutrition, which was mainly caused by the tumor itself that directly impeded oral intake. In addition to tumor-related factors, patients with impairment in physical activity, cognitive defects, and lack of social support might also be prone to malnutrition.[47] Therefore, we believe that frailty status, which shows the accumulation of multiple functional deficits, might be more reliable than

performance status alone in predicting treatment tolerance and survival outcome in patients with cancer.

As our study revealed that frailty assessment has prognostic significance among younger patients with HNC and EC, the frailty assessment provides an objective means to identify patients more susceptible to treatment toxicity. Furthermore, while our study also identified patients who are more likely to have treatment incompletion, identification of frail patients is important for a more tailored treatment plan. Thus, we advise GA among all patients with HNC and EC. Purpose of anticancer treatment has been to prolong life while maintaining a balance between treatment toxicity and quality of life. Hospitalization and treatment discontinuation are both reflection of intolerance to treatment toxicity which would lead to deprived quality of life. As our study has shown more frequent hospitalization and treatment discontinuation from the frail group, benefits of curative-intent CCRT may be more limited or treatment should be more tailored to balance the foreseen toxicity.

This is the largest prospective study to date in the evaluation of the frail assessment's prognostic efficacy in a younger population of specific cancer undergoing definitive treatment. However, this study had several limitations. First, the aspects and instruments of frailty assessment in younger oncologic patients are still debatable and not validated.[11] Not surprisingly, cognition and mobility/falls were the least prevalent functional defects in our cohort. The diagnosis of frailty in non-elderly patients might likely be underestimated based on GA. Although the impairment of function domains might differ among older and younger populations, our study exhibited frailty assessment by GA, as the accumulation of multiple functional deficits is a reliable tool for predicting treatment-related complications and survival outcomes in younger patients with cancer. Second, frail patients in our cohort had poor survival outcomes; however, this may be due to poor performance and a higher percentage of primary tumors other than the nasopharynx than those in the fit patient group. However, the impact of frailty on survival outcome remained after adjustment for other confounding factors in the multivariate analysis. Finally, and most importantly, frailty assessment should include the evaluation of functional impairment followed by subsequent intervention for the frail dimension. This study provided only a proof-of-concept that the use of pretreatment frail assessment may help guide decision-making regarding antitumor treatment in younger patients. Further studies are necessary to evaluate whether appropriate frail intervention might overcome treatment-related toxicities and improve survival outcomes for frail patients.

Conclusion

This study presented the significance of pretreatment frailty on treatment tolerance, treatment-related toxicity, and survival outcome in younger patients with HNC and EC undergoing CCRT. While GA is commonly targeted toward the older population, our data showed that frailty assessment using GA may also be utilized in younger patients for decision-making guidance and prognosis prediction. GA should be incorporated into clinical practice for each patient, regardless of age, with locally advanced HNC and EC before the initiation of intensive cancer therapy.

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Author Contributions

Conception and design of study: CWC, LCC, and HCY; acquisition of data: HSW, YKY, and LCH; analysis and interpretation of data: TNM, CPH, HYW, CSY, LYC, and HYS; and drafting of the manuscript: CWC, LCC, HCY, HSW, YKY, LCH, TNM, CPH, HYW, CSY, LYC, and HYS.

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital in August 2017 (ethic code: 1608080002) and has been conducted in compliance with the Helsinki Declaration (1996).

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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