Glasgow prognostic score after concurrent chemoradiotherapy is a prognostic factor in advanced head and neck cancer

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Abstract

Objective: This study aims to evaluate the impact and potential prognostic roles of the pre- and post-treatment Glasgow prognostic score (GPS) and the change thereof in patients with advanced head and neck cancer undergoing concurrent chemoradiotherapy (CCRT).

Methods: We collected GPS and clinicopathological data of 139 stage III, IVA, and IVB head and neck cancer patients who underwent CCRT between 2008 and 2011. Their GPSs pre- and post-CCRT and the change thereof were analyzed for correlations with recurrence and survival.

Results: The GPS changed in 72 (51.8%) patients, with worse scores observed post-CCRT in 65 (90.3%) of the GPS changed patients. Patients in the improved GPS group showed a tendency toward better survival. From the multivariate analysis, the post-CCRT GPS level was an independent prognostic factor in addition to tumor stage.

Conclusions: After CCRT, a high GPS was revealed to be an important predictor of survival for advanced head and neck cancer.

Keywords: Glasgow prognostic score (GPS); head and neck cancer; chemoradiation; inflammation; cachexia; nutrition

Introduction

Concurrent chemoradiotherapy (CCRT) has become one of the standard therapies for patients with locally advanced head and neck cancer and has been demonstrated to result in significant improvements in the survival and disease control rates compared to radiation alone (1). Importantly, CCRT-induced toxicities, including emesis, anorexia, mucositis, dysphagia and xerostomia, have a negative impact on the nutrition status and functional abilities of the patients, thereby compromising the treatment tolerance and efficacy, and increasing healthcare costs (2). Malnutrition before CCRT is associated with increased risks of complications, toxic deaths, and poor survival (3,4). Hence, early and intensive nutrition support during CCRT is important and may be beneficial for minimizing body

weight loss, potentially resulting in better treatment tolerance and survival benefits in advanced head and neck cancer undergoing CCRT, as demonstrated in a previous study (5).

There is an increasing recognition that patient-related factors, especially nutritional and functional declines, are correlated with poorer outcome in addition to the tumor stage. The inflammation-based Glasgow prognostic score (GPS) has been used to reflect the degree of tumor-associated inflammation and malnutrition (6), with patients with an elevated GPS considered to have pre-cachexia (7). Thus, it is reasonable to use the GPS as a biomarker for malnutrition surveillance. Further, the pretreatment GPS has been shown to be a prognostic factor in head and neck cancer (8), with the overall survival (OS) and recurrence-free survival (RFS) being higher when the GPS was low.

CCRT is known to have a negative impact on nutritional status (2,9). However, to our knowledge, changes in the GPS after CCRT relative to the pretreatment GPS have never been investigated, and the prognostic impact of post-CCRT GPS remains unknown. Therefore, the aims of this study were to evaluate the changes in the GPS during CCRT and the impact and potential prognostic roles of the pre- and post-treatment GPSs and the change thereof in patients with advanced head and neck cancer undergoing CCRT.

Materials and methods

Patient selection

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Patients with biopsy-proven stage III, IVA, or IVB head and neck squamous cell carcinoma [TNM stage reclassified according to the American Joint Committee on Cancer (AJCC) staging system published in 2002] of the oral cavity, oropharynx, and hypopharynx, and who were treated with primary CCRT were eligible for this study. Patients with recurrent cancer, distant metastasis, another concomitant active cancer, or toxic death during the treatment course were excluded from the study. We retrospectively reviewed the records of 161 patients with stage III, IVA, and IVB head and neck squamous cell carcinoma who underwent CCRT at the Department of Internal Medicine, Chang Gung Memorial Hospital between January 2008 and December 2011. All patients were followed up until March 2015. Twenty-two patients were excluded from the study. Ten

patients dropped out during the CCRT regimen and were lost to follow-up because of unavoidable family reasons, such as poor financial support (6 patients) and moving out of town (4 patients). Six patients died during the treatment course. Four patients were treated with re-chemoradiation for recurrent disease and two were diagnosed with a concomitant active cancer upon diagnosis. Thus, 139 patients receiving CCRT were included in the final analysis. All patients received intensity-modulated or arc technique radiotherapy on 5 consecutive days per week at a conventional fractionated daily dose of 1.8 or 2 Gy. The total prescribed dose of radiotherapy was 70–74 Gy. The initial treatment volume included the tumor bed and regional lymphatics. After receiving 46–50 Gy, the treatment area was reduced to irradiate the tumor bed and regional nodes. The chemotherapy regimens, which included cisplatin 40 mg/m² every week or 100 mg/m² every 3 weeks, were administered according to the treatment guidelines at the Department of Internal Medicine, Chang Gung Memorial Hospital. All patients are required to place the feeding tube placement including nasogastric tube or percutaneous gastrostomy if their weight loss is more than 5% during treatment period.

Data collection

The following clinical and demographic parameters were retrospectively analyzed in this study: age, gender, primary site of disease, TNM stage at diagnosis (AJCC), Eastern Cooperative Oncology Group performance status, and serum albumin and C-reactive protein (CRP) levels before and at the end of the treatment. The treatment outcomes were assessed by the RFS and OS rates. RFS was defined as the time from the initiation of CCRT to the first evidence of recurrence of the primary tumor. OS was defined as the time from the initiation of CCRT to death from any cause.

GPS

The GPS was calculated as follows in our study: patients with elevated serum CRP (>10 mg/L) and hypo-albuminemia (<3.5 mg/L) were allocated a score of 2, patients with only one of these biochemical abnormalities were allocated a score of 1, and patients with neither of these abnormalities were allocated a score of 0.

Statistical analysis

Statistical analyses were performed using IBM SPSS

Statistics (Version 19.0; IBM Corp., New York, USA). The Kaplan-Meier method was used to analyze survival, and the log-rank test was used to examine the differences in survival between the study groups. Multivariate analysis was performed using Cox's proportional hazards model. Differences were considered statistically significant when $P<0.05$.

Results

Study population

The baseline characteristics of the study patients are shown in Table 1. Among the 139 patients who underwent CCRT for advanced head and neck cancer during the study period,

Table 1 Demographic characteristics of patients who underwent CCRT for advanced head and neck cancer (N=139)

Variables	n (%)
Age (year) ($\bar{x}\pm s$)	54.5±11.5
Gender	
Male	127 (91.4)
Female	12 (8.6)
T classification	
T1	11 (7.9)
T2	28 (20.1)
T3	33 (23.7)
T4	67 (48.2)
N classification	
N0	34 (24.5)
N1	20 (14.4)
N2	72 (51.8)
N3	13 (9.4)
TNM classification	
III	29 (20.9)
IVA, B	110 (79.1)
Tumor site	
Oral cavity	50 (36.0)
Oropharynx	51 (36.7)
Hypopharynx	38 (27.3)
ECOG performance status	
0, 1	115 (82.7)
2	24 (17.3)

CCRT, concurrent chemoradiotherapy; T, tumor; N, node; TNM, tumor, node, metastasis; ECOG, Eastern Cooperative Oncology Group.

the age at diagnosis ranged from 26 to 79 years (median, 53 years), and the dominant gender was male (91.4%). Twenty-nine (20.9%) and 110 (79.1%) patients were diagnosed with stage III and IVA–B disease, respectively. Figure 1 shows the changes in the GPS after CCRT as compared to the pretreatment values. The number of patients with pretreatment GPSs of 0, 1 and 2 were 32 (23.0%), 72 (51.8%) and 35 (25.2%), respectively. Of all patients, 72 (51.8%) showed changes in the GPS after CCRT; the GPS worsened in 65 (46.8%) patients and was improved in only 7 (5.0%) patients. After CCRT, the numbers of patients with GPSs of 0, 1, and 2 were 9 (6.5%), 46 (33.1%), and 84 (60.4%), respectively (Figure 1).

Survival analysis according to GPS

After a median follow-up duration of 38 (interquartile range, 5.9–62.3) months, there were 70 (50.4%) and 62 (44.6%) cases of disease recurrence and death, respectively. The OS according to the pre- and post-CCRT GPSs are shown in Figure 2A, B. There were significant difference in the OS according to both the pre-CCRT GPS (P=0.010) and post-CCRT GPS (P<0.001). We further classified the patients into three groups according to the changes in the GPS after CCRT relative to at pretreatment (improved, conserved, and worse GPS). There was no death in the improved GPS group. The highest OS was observed in the improved GPS group, while the lowest OS was observed in the worse GPS group. The group with improved GPS had a higher OS rate compared to the worse GPS group (P=0.013) (Figure 2C). Similar results were observed for the relationship between RFS and GPS. Patients with a GPS of
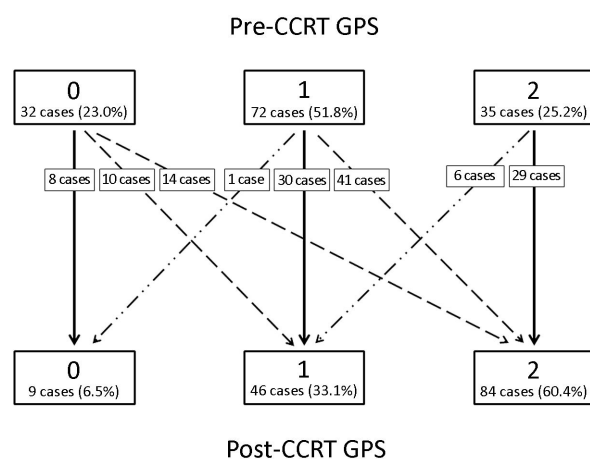

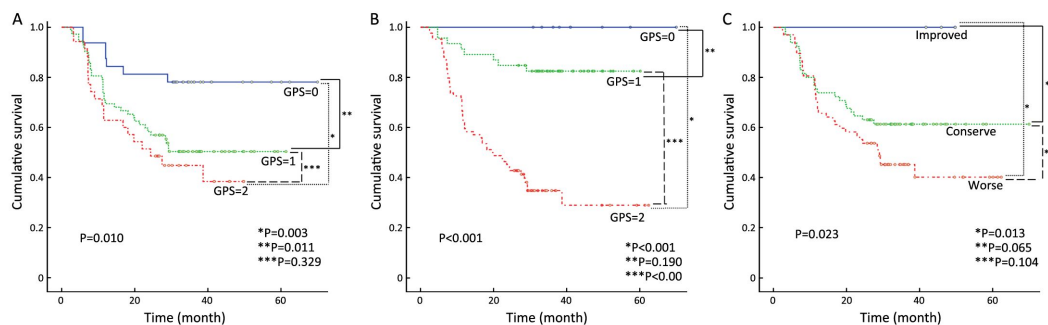**Figure 1** Changes in Glasgow prognostic score (GPS) after concurrent chemoradiotherapy (CCRT).

Figure 2 Overall survival (OS) of patients with different Glasgow prognostic score (GPS). Censored observations are indicated by the points on the curves. (A) Comparison among patients with different GPS before concurrent chemoradiotherapy (CCRT); (B) Comparison among patients with different GPS after CCRT; (C) Comparison among patients according to the change in GPS after CCRT.

0 had significantly better RFS when classified according to the pre-CCRT (P=0.025) and post-CCRT GPS scores (P<0.001) (*Figure 3A*, *B*). When classified according to the changes in the GPS after CCRT relative to the pretreatment GPS, the highest and lowest RFSs were observed in the groups with improved and worse GPSs, respectively. The group with improved GPS showed a higher RFS rate compared to the group with worse GPS (P=0.012) and conserve GPS (P=0.032) (*Figure 3C*). When the pretreatment GPS, posttreatment GPS, change in GPS, tumor stage, tumor site, patient age, patient gender and patient performance status were analyzed as prognostic scores for RFS and OS by multivariate analysis, the post-CCRT GPS was shown to be an independent prognostic parameter, in addition to tumor stage (*Table 2*).

Discussion

Tumor stage is widely accepted as the cornerstone of cancer prognosis. However, there is increasing evidence that patient-related factors, such as nutritional and functional declines, are associated with a poorer prognosis, independent of the tumor stage. Several reports have demonstrated that the presence of a systemic inflammatory response is associated with increased weight loss, elevated resting energy expenditure, loss of lean tissue, and functional decline (10-14). Cancer cachexia is associated with complex metabolic, molecular, and cellular alterations, and an increased plasma level of CRP, combined with reduced food intake and weight loss, has been used as a clinical marker of cancer cachexia (15). In addition, inflammation appears to also play a significant role in cancer anorexia. In animal models of cancer anorexia, increased brain levels of various cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) have been demonstrated (16,17), and blocking of circulating TNF-α or intra-hypothalamic IL-1 receptors in anorexic tumor-bearing mice has been shown to improve food intake (18,19). Further, serum albumin is known to correlate with systemic inflammation through increased
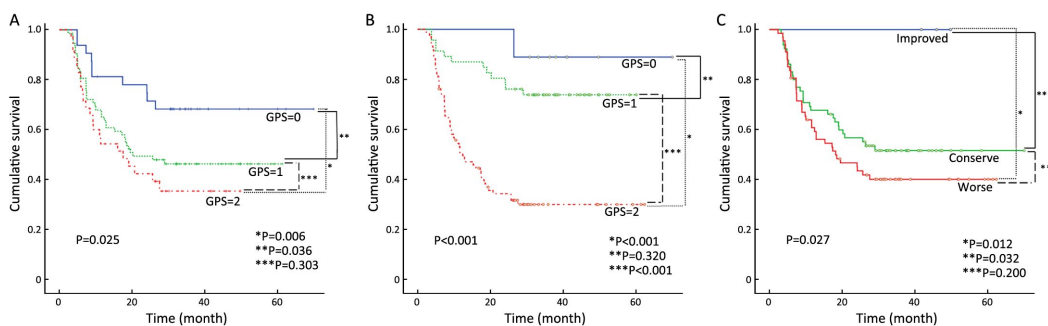

Figure 3 Recurrence-free survival (RFS) of patients with different Glasgow prognostic score (GPS). Censored observations are indicated by the points on the curves. (A) Comparison among patients with different GPS before concurrent chemoradiotherapy (CCRT); (B) Comparison among patients with different GPS after CCRT; (C) Comparison among patients according to the change in GPS after CCRT.

Table 2 Multivariate survival analysis in 139 patients

Variables	RFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Age (year) (≥65, <65)	1.019 (0.992–1.047)	0.173	1.008 (0.981–1.036)	0.561
Gender (female, male)	1.172 (0.477–2.881)	0.729	1.004 (0.304–3.310)	0.906
Tumor site (OC, OPX, HPX)	1.026 (0.702–1.497)	0.659	1.118 (0.789–1.568)	0.516
AJCC TNM stage (III, IV)	4.182 (1.623–10.773)	0.003	6.041 (1.976–18.467)	0.002
Performance status (0, 1, 2)	1.093 (0.559–2.137)	0.513	1.361 (0.890–2.688)	0.374
Histological differentiation (well, moderate, poor)	1.153 (0.832–1.598)	0.393	1.292 (0.909–1.838)	0.154
Radiation dose (cGy) (≥6,300, <6,300)	1.651 (0.983–2.771)	0.068	1.564 (0.904–2.703)	0.109
Pre-CRT GPS score (0, 1, 2)	1.108 (0.531–2.311)	0.393	2.076 (0.468–2.145)	0.136
Post-CRT GPS score (0, 1, 2)	3.518 (1.359–9.106)	0.010	4.419 (1.548–12.613)	0.029
GPS change (improved, conserve, worse)	1.207 (0.424–3.213)	0.968	1.684 (0.549–5.167)	0.701

RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; OC, oral cavity; OPX, oropharynx; HPX, hypopharynx; AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; GPS, Glasgow prognostic score.

levels of pro-inflammatory cytokines. Increased catabolism, chronic malnutrition, and chronic inflammatory reactions due to cancer eventually lead to hypoalbuminemia, which has been shown to be associated with poor survival in various cancers (20). The GPS is calculated from the serum CRP and albumin concentrations. It is simple to measure, routinely available, and well-standardized worldwide; as a result, it has been the subject of prognostic studies in a wide variety of cancers (10). MacDonald *et al.* (7) reported that the prognosis of patients with an elevated GPS was extremely poor and that these patients should thus be given pre-cachexia status and offered multimodal therapy, which may delay the onset of cachexia and death. McMillan *et al.* (10) concluded that the GPS may be included in addition or in preference to the current definitions of cachexia, along with tumor staging as part of the routine assessment of all cancer patients. As a consequence, using GPS as an objective prognostic nutritional marker is considered reasonable.

The majority of patients (51.8%) in our study showed changes in the GPS after CCRT. Of patients with changes in the GPS, 65 of 72 patients (90.3%) had a worsened GPS post-CCRT. This result implies that most patients' nutritional status declined after CCRT, since GPS reflects the degree of malnutrition (6). We further analyzed the relationship between the GPS change and survival. The results showed that patients with improved GPS tended to have better OS (P=0.013) and RFS (P=0.012) compared with those with worse GPS (*Figure 2C*, *3C*). These findings

suggest that we need to pay attention to the GPS, and that maintaining or improving the patients' nutritional status is critical during CCRT. Furthermore, our findings also demonstrated that a higher pretreatment GPS was associated with poor disease-free survival (DFS) and OS, which is in accordance with a previous study reported by Nakayama *et al.* (8). Since the GPS can reflect the degree of cachexia and malnutrition (6), and considering that the post-CCRT GPS declined in most patients in our study, we further analyzed the prognostic role of post-CCRT GPS as a biomarker for the follow-up of the patients' nutritional status and found that the post-CCRT GPS level was an independent prognostic factor in the multivariate analysis, rather than the pre-CCRT GPS (*Table 2*), implying that poor nutrition after CCRT can predict survival.

To our knowledge, the changes in the GPS after treatment and the association between the post-CCRT GPS and survival outcome have never been investigated previously, and these factors deserve further discussion. In our study, the post-CCRT GPS was a better prognostic factor than the pre-CCRT GPS. Using the GPS as a nutritional prognostic marker, our study showed that malnutrition after CCRT was associated with poor survival outcome. Accordingly, the malnutrition status following therapy completion deserves more attention, and evaluating the treatment influence on patient outcomes following effect-induced malnutrition is important.

The post-treatment effects of CCRT on the nutrition

status are often long-lasting (21). Therefore, nutrition surveillance should continue during the recovery and follow-up period to ensure adequate nutrition intake. However, the post-CCRT nutrition status is often overlooked, and thus, the efficacy of curative therapy may be compromised, consequently leading to undue adverse effects and potentially shortened duration of life. In a previous study, low body mass index at 3 months following CCRT completion was found to strongly associate with poorer survival outcomes (22). Taken together with our study results, this indicates that special attention should be paid continuously, from pretreatment to post-treatment, to the nutrition status of patients undergoing CCRT, and that an intensive nutritional intervention schedule should be implemented and maintained. Yeh *et al*. (23) conducted a randomized study and reported that the addition of several micronutrients and probiotics to an omega-3 fatty acid containing oral nutritional supplement improved the maintenance of body weight, serum albumin, and prealbumin levels in head and neck cancer patients with cachexia who were undergoing CCRT. Nutrient support, via eicosapentaenoic acid (EPA) food components, therefore attracted attention as a potential anti-tumor immunonutrition therapy and is a potential treatment strategy to improve GPS. As shown in this study, improving GPS may therefore help improve patients' survival in advanced head and neck cancer patients who are undergoing CCRT. Hence, further large-scale prospective studies are required to fully determine how to reduce the worsening of the GPS during CCRT in order to improve patients' outcomes.

Some limitations of this study should be acknowledged. First, this study was a retrospective study, conducted in a single institute without blindness or control groups. Second, the number of patients studied was small. Only 7 patients were in the improved GPS group for analysis. In the future, larger prospective studies are needed to establish the significance of the GPS in advanced head and neck cancers.

Conclusions

Nutritional intervention and maintenance before, during, and especially after CCRT are important and affect the survival of patients with advanced head and neck cancer undergoing CCRT. GPS is an objective prognostic nutritional marker for survival and provides additional value in these patients and should hence be included in clinical practice.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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