

The Glasgow prognostic score: Useful information when prescribing palliative radiotherapy

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Abstract. The purpose of the present retrospective study was to investigate whether a score reflecting systemic inflammatory processes [the Glasgow Prognostic Score (GPS)] provides relevant information for radiation oncologists. GPS is a three-tiered score [0: normal C-reactive protein (CRP) and albumin; 1: one abnormal result; 2: increased CRP and low albumin]. Correlations between disease type and extent, resource utilization, survival and GPS were analyzed in 703 patients. In the subgroup with GPS 2, significantly higher rates of lung, adrenal gland and liver metastases were observed. An increasing GPS score was associated with a higher likelihood of anemia, leukocytosis and thrombocytosis. Comparable findings were made regarding utilization of palliative care resources, need for blood transfusion and intravenous administration of antibiotics. Compared with GPS 0 or 1, more patients with GPS 2 did not complete their prescribed course of radiotherapy. One-third of patients with GPS 2 received treatment during the final month of life. Multivariate analysis demonstrated that GPS was a significant prognostic factor for overall survival (median, 479, 136, and 61 days, for GPS 0, 1 and 2, respectively). In patients with GPS 2 and additional leukocytosis, the median survival was 38 days. In conclusion, GPS provides important prognostic information. This biomarker-based score may be considered for deciding fractionation, and should be validated further.

Introduction

Prognostic information is essential when choosing between treatment regimens with different levels of intensity, and when stratifying patients who participate in clinical studies. Often,

different items, which contribute information, are combined into a clinically useful tool, e.g., a staging system or prognostic score (1). In patients with progressive cancer, the prognosis changes during the disease trajectory (2). If an assessment could be based on factors that are easy to measure and inexpensive, clinical decision-making would be improved, particularly in low-income countries with limited health care resources. In this context, the Glasgow prognostic score (GPS) might be an excellent tool (3). It is based on measurement of the levels of serum albumin and C-reactive protein (CRP), reflects inflammatory processes that may perpetuate tumor progression, and has been shown to correlate with survival in patients with lung, gastrointestinal, prostate and renal cancer (4-6). Surprisingly little research has been performed regarding its potential role in patients who receive palliative radiotherapy. As the role of palliative radiotherapy in patients with very short survival has recently come under scrutiny (7-9), in the present study, the ability of GPS to predict survival in a large contemporary cohort of patients was examined.

Patients and methods

A retrospective analysis of the records of 873 consecutive patients with metastatic or otherwise incurable cancer who received palliative radiotherapy at a single institution (Nordland Hospital, Bodø, Norway) was performed. Due to their different biological behavior, hematological and primary brain malignancies were not included. Treatment was initiated during the time period between 20 June 2007 (the date of opening of the institution's radiotherapy facility) and 31 December 2011. Medical records and treatment details were abstracted from the hospital's electronic patient record (EPR) system. The survival status and date of death, or last follow-up, of the patients were obtained from the EPR during September 2014, resulting in at least 2.5 years of follow-up for surviving patients. IBM SPSS Statistics 21.0 (IBM SPSS, Armonk, NY, USA) was used to evaluate the association between survival, GPS and other prognostic factors. Only blood test results obtained within 1 week prior to the radiotherapy were considered. For albumin, the institutional lower limit was 36 g/l. The cut-off for CRP was 8 mg/l. Overall, 703 patients had available blood tests, and were eligible for the present study. The Eastern Cooperative Oncology Group

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(ECOG) performance status (PS) was registered routinely at the time of consultation in conjunction with radiotherapy (10). Actuarial survival curves from the first day of radiotherapy were generated using the Kaplan-Meier method, and compared using the log-rank test. For multivariate analysis of survival, Cox regression analysis was used (the forward stepwise method). All factors with a significant P-value in univariate log-rank tests were carried forward to multivariate regression analysis. Associations between different variables of interest were assessed with the Chi-square and Fisher exact probability tests. In two-sided tests, $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics in 703 patients. The median age was 68 years (range, 31-95 years). The median time from first cancer diagnosis to palliative radiotherapy was 2 years (range, 0-30 years). In patients with distant metastases, the median interval between diagnosis of metastatic disease and palliative radiotherapy was 7 months (range, 0-149 months). Common treatment indications included skeletal metastases (57%), brain metastases (16%), thoracic symptoms from lung cancer (12%), and lymph node metastases (9%). The most common fractionation regimen was 3 Gy x 10 (45%), followed by 5-7 fractions of 4 Gy (22%) and single-fraction 8 Gy x 1 (8.5 Gy x2 for lung cancer) in 15% of the cases. Stereotactic radiotherapy was not available. The majority of the patients had prostate cancer (26%), non-small cell lung cancer (NSCLC, 22%) or breast cancer (13%) as primary tumors.

GPS reflects prognostically important disease characteristics. A total of 34% of the patients had normal CRP and albumin scores (GPS 0). Of the total patients, 19% had abnormal CRP and albumin (GPS 2). The remaining 47% of the patients had GPS 1 (in 96% of cases resulting from an elevated level of CRP; in 4%, due to a low level of albumin). As shown in Table I, the majority of the patients with GPS 0 had a good PS (ECOG 0 or 1), whereas most patients with GPS 2 had a poor PS (ECOG 3 or 4; $P = 0.0001$). Significant differences were also observed regarding the primary tumor type. Primary tumors that were frequently associated with GPS 2 were pancreatic cancer (40% of these patients had GPS 2), bladder cancer (30%), colorectal cancer (28%), and NSCLC (26%). The pattern of metastatic disease also correlated with GPS. Patients with GPS 2 had markedly higher rates of adrenal gland, lung and liver metastases. Increasing levels of GPS were correlated with an increasing likelihood of documented disease progression outside of the radiotherapy target volumes(s) at the time of the last assessment prior to radiotherapy ($P = 0.0001$). Anemia was more common in patients with a higher GPS ($P = 0.0001$). Comparable correlations were detected for leukocytosis and high platelet counts ($P = 0.0001$). Increasing GPS was also associated with a low level of serum creatinine, a surrogate marker of reduced muscle mass, or cachexia ($P = 0.0001$).

GPS reflects resource utilization and predicts early death. As shown in Table II, GPS was associated with the utilization of palliative care resources, the number of blood transfusions and intravenous treatment with antibiotics. A larger proportion of the patients with GPS 2 were unable to complete their

prescribed course of radiotherapy. One-third of patients with GPS 2 received palliative radiotherapy in the terminal phase (final month of life). Patients with GPS 2 were less often treated with long-course radiotherapy, defined as ≥ 10 fractions (46%, compared with 62% in the subgroup with GPS 1, and 72% of those with GPS 0; $P = 0.0001$).

Survival. The median survival rate was 183 days (6 months). As shown in Fig. 1, GPS significantly correlated with survival (median 479, 136, and 61 days, respectively, for GPS 0, 1 and 2; $P = 0.0001$). Therefore GPS was entered into a multivariate Cox regression model, together with all the other prognostic factors, which achieved a P -value < 0.05 in univariate log-rank tests [age as a continuous variable, ECOG PS, primary tumor type, anemia, leukocytosis, low serum creatinine, progressive disease outside of target volume(s), brain metastases, liver metastases, lung metastases, bone metastases, and adrenal gland metastases]. Seven out of these 13 variables were revealed to be independent prognostic factors for survival: GPS, ECOG PS, brain metastases, liver metastases, bone metastases, progressive disease outside of target volume(s), and leukocytosis (all with $P \leq 0.001$).

On the one hand, the median survival of patients with GPS 2 was short, and administration of radiotherapy during the last month of life was not unusual. On the other hand, survival in this subgroup was too heterogeneous to conclude that all these patients were poor candidates for radiotherapy. An appreciable number of them survived long enough to benefit from and experience symptom improvement. Thus, additional variables are required in order to define a subgroup with uniformly short survival. As mentioned above, these variables should be easy to assess and inexpensive in order to decide upon which model would be applicable to practice settings in countries with limited resources. Factoring in ECOG PS was clearly a way forward. Figs. 2 and 3 show the usefulness of combining GPS and ECOG PS, at least in patients with GPS 0 and 1. However, in the relevant target group of patients with GPS 2, the survival data did not reveal significant differences (Fig. 4). Table III shows the median survival of patients with different ECOG PS stratified by GPS. The two groups with the shortest survival rates were patients with ECOG PS 3 and GPS 2, and patients with ECOG PS 4, irrespective of GPS. The second variable not requiring any additional resources (such as, e.g., imaging) was leukocytosis. This may be evaluated from the drawing of the same blood required to assign GPS. As shown in Fig. 5, patients with GPS 2 and leukocytosis had a median survival of 38 days, as compared with 89 days in those with a normal leukocyte count ($P = 0.007$). Only 20% of the patients with three abnormal biomarkers were alive after 3 months. Comparable associations were observed in patients with GPS 1 (median, 94 vs. 192 days) and GPS 0 (median, 162 vs. 635 days).

Models with a different CRP cut-off. GPS does not take into account the magnitude of CRP increase: Assignment is based solely on normal vs. increased CRP. Therefore, the analyses in the present study were expanded, and different levels of an increase in CRP (30, 60 or 90 mg/l) were examined. However, survival prediction did not improve in these analyses requiring certain levels of an increase in CRP (results not shown). Albumin levels were less variable. Almost all patients with low levels of albumin had measurements of 30-35 g/l. Therefore, stratified analyses could not be meaningfully performed.

Table I. Baseline characteristics stratified by GPS scores of the patients (n=703).

Parameter	0	%	1	%	2	%	P-value
Gender							
Female	90	37	114	35	48	37	0.77
Male	151	63	216	65	83	63	
Age, years							
<60	47	20	71	21	24	18	0.7
≥80	38	16	44	13	20	15	0.46
ECOG PS							
0	41	17	35	11	2	2	0.0001
1	111	46	98	30	10	8	
2	63	26	124	37	46	35	
3	25	10	61	18	63	48	
4	0	0	13	4	10	8	
Type of cancer							
Prostate cancer	91	38	71	21	21	16	0.0001
Breast cancer	43	18	31	9	15	11	
Non-small cell lung cancer	34	14	82	25	41	31	
Small cell lung cancer	15	6	24	7	4	3	
Colorectal cancer	10	4	23	7	13	10	
Pancreatic cancer	1	0	5	2	4	3	
Bladder cancer	7	3	24	7	13	10	
Malignant melanoma	9	4	11	3	2	2	
Kidney cancer	11	5	35	11	8	6	
Other primary tumor	20	8	25	8	10	8	
Metastases							
Bone ^a	162	68	222	67	102	78	0.06
Brain ^a	50	21	67	20	22	17	0.61
Liver ^a	40	17	77	23	37	28	0.028
Lung ^a	41	17	97	29	46	35	0.0001
Adrenal ^a	14	6	38	11	25	19	0.0001
No distant	28	4	34	5	8	1	0.23
Progressive disease outside of RT field	97	42	189	58	90	73	0.0001
Anemia ^b	101	42	223	68	116	89	0.0001
Leukocytosis ^c	31	13	83	25	56	44	0.0001
Thrombocytosis ^d	34	14	105	33	50	40	0.0001
Serum creatinine							
Low ^e	16	2	49	7	36	5	0.0001 ^e
High ^e	27	4	58	8	19	3	
No previous systemic therapy	88	39	131	42	58	48	0.26

^aPresent, but not necessarily treated by RT; ^bhemoglobin below the normal institutional limit; ^cleukocyte count above institutional normal limit; ^dthrombocyte count (platelets) above institutional normal limit; ^ecreatinine below/above institutional normal limit; efor all three strata (low/normal/high). ECOG, Eastern Cooperative Oncology Group; PS, performance status; GPS, Glasgow Prognostic Score; RT, radiotherapy.

Discussion

Irrespective of the health care setting, increasing expenses and limited budgets create serious challenges for the oncology community. Initiatives such as the 'Choosing Wisely' campaign (11) are trying to provide support to stakeholders, who are required to discriminate between cost-effective

interventions and imprudent resource utilization. Although palliative radiotherapy, in general, is considered excellent value for money, the large number of available fractionation regimens and techniques, and the broad spectrum of survival outcomes, make it difficult to always ensure that the correct treatment is assigned to the right patient (12). Staging systems and prognostic scores play an invaluable role when assessing

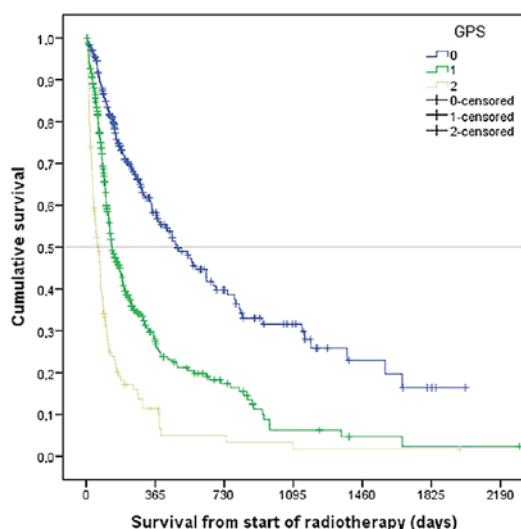


Figure 1. Actuarial overall survival after palliative radiotherapy stratified by GPS ($P=0.0001$, log-rank test). The number of patients was 241, 331, and 131 for GPS 0, 1 and 2, respectively. GPS, Glasgow prognostic score.

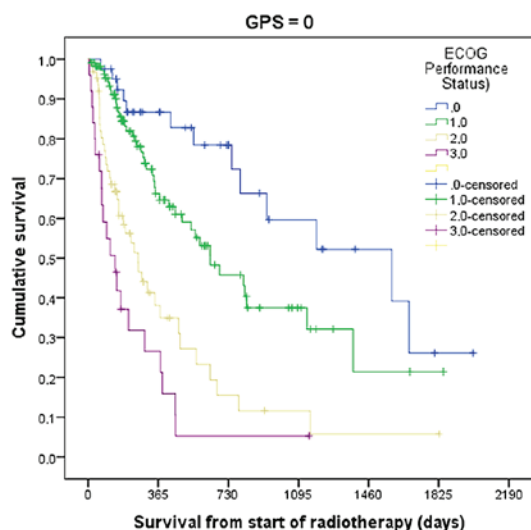


Figure 2. Actuarial overall survival following palliative radiotherapy in patients with GPS 0 stratified by ECOG performance status ($P=0.0001$, log-rank test). The number of patients was 41, 111, 64, and 25 for ECOS performance statuses of 0, 1, 2 and 3, respectively. GPS, Glasgow prognostic score; ECOG, Eastern Cooperative Oncology Group.

individual patients and making treatment recommendations, as demonstrated by the broad adoption of brain metastases scores (13,14). Particularly in patients with a limited survival expectation, decision making should not require comprehensive and expensive restaging, which could also delay the initiation of meaningful palliative interventions. These considerations are even more relevant for low-income countries. Widely available routine blood tests may provide excellent prognostic information, and value for money (15), since results are available within a few hours.

During the last decade, an inflammation-based prognostic score, GPS, has been studied in different oncology settings, e.g., in chemotherapy for NSCLC and prostate cancer (3,6). This research suggests that malnourished cancer patients had a statistically significant higher CRP, neutrophil-to-lymphocyte ratio

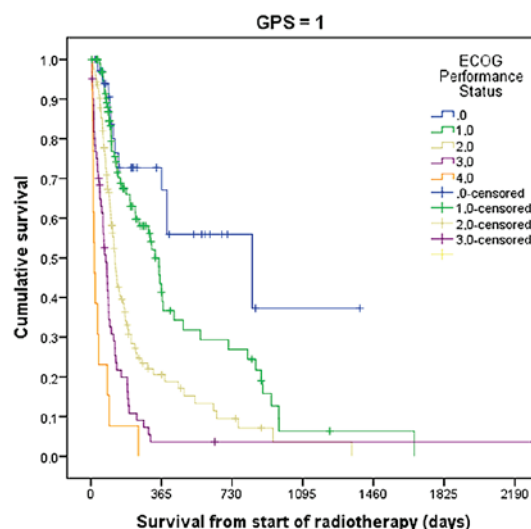


Figure 3. Actuarial overall survival following palliative radiotherapy in patients with GPS 1 stratified by ECOG performance status ($P=0.001$, log-rank test). The number of patients was 35, 98, 124, 61, and 13 for ECOS performance statuses of 0, 1, 2, 3, and 4, respectively. GPS, Glasgow prognostic score; ECOG, Eastern Cooperative Oncology Group.

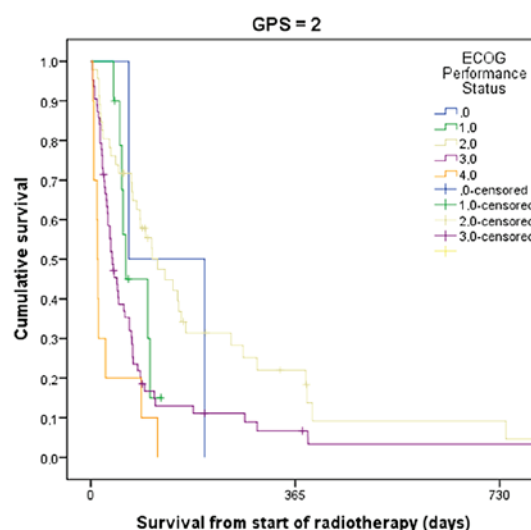


Figure 4. Actuarial overall survival following palliative radiotherapy in patients with GPS 2 stratified by ECOG performance status ($P=0.3$, log-rank test). The number of patients was 2, 10, 46, 63, and 10, for ECOS performance statuses of 0, 1, 2, 3, and 4, respectively. GPS, Glasgow prognostic score; ECOG, Eastern Cooperative Oncology Group.

and GPS prior to starting the chemotherapy (16). Eventually, it was shown that GPS predicts cancer survival independently of the tumor site (4). Limited data are available regarding GPS and radiotherapy (17). The latter study focused on the end-of-life care, and identified that GPS 2 was strongly associated with the receipt of radiotherapy during the last 30 days of life. The present study, to the best of the authors' knowledge, is the first comprehensive analysis of GPS in a large cohort of patients who received palliative radiotherapy. GPS was assigned retrospectively, and not used during the time period of actual patient treatments. Only a minority of patients (34%) had normal CRP and albumin, i.e., GPS 0. Strong associations between GPS and ECOG PS were identified, comparable with earlier

Table II. Resource utilization and treatment completion stratified by GPS scores of the patients (n=703).

Endpoint	0	%	1	%	2	%	P-value
Received blood transfusion during RT	2	1	17	5	15	12	0.0001
Received iv antibiotics during RT	7	3	34	11	28	23	0.0001
Care by palliative team during RT	38	17	75	24	42	37	0.0001
Pain management with continuous infusion pump	2	1	14	4	17	13	0.0001
Incomplete RT	4	2	21	6	17	13	0.0001
RT during last month of life	8	3	33	10	43	33	0.0001

RT, radiotherapy; iv, intravenous.

Table III. Median survival (days, 95% confidence interval) in patients with different PSs stratified by GPS scores (n=702).

ECOS PS	No. of patients	0	1	2
0	78	1,580 (686-2,474)	833 (58-1,608)	68 (n/a; only 2 patients)
1	219	636 (372-900)	332 (275-389)	63 (49-77)
2	233	261 (163-359)	126 (107-145)	120 (70-170)
3	149	140 (57-223)	78 (57-99)	39 (26-52)
4	23	No patients	19 (7-31)	12 (9-15)

ECOG, Eastern Cooperative Oncology Group; PS, performance score; n/a, not applicable.

reports (18). It is tempting to speculate that GPS is merely a surrogate marker of tumor extent and tumor-host interactions, since GPS correlated with progression, the pattern of metastatic disease, anemia, leukocytosis and thrombocytosis. However, in multivariate analysis of prognostic factors for overall survival that included all these variables, the added value of GPS was confirmed. This finding is in line with non-radiotherapy studies (5,19,20). Due to its robust prognostic value, low cost and wide availability, additional studies of GPS in different radiotherapy settings are recommended.

Previous studies also found significant associations between GPS and the chemotherapy dose adjustment, the requirement for granulocyte colony-stimulating factor support, termination of treatment due to side-effects, and fatal toxicity (21). In the present study, GPS was associated with more frequent utilization of palliative care resources, the number of blood transfusions and intravenous treatment with antibiotics. Compared with patients with GPS 0 or 1, more patients with GPS 2 were not able to complete their prescribed course of radiotherapy. A total of 33% of the patients with GPS 2 received treatment during the final month of their life. It is therefore important to consider short-course (e.g., 8.5 Gy x 2, 4 Gy x 5) and single-fraction (8 Gy) radiotherapy regimens in patients with GPS 2. The development of prediction models specifically for the purpose of avoidance of too aggressive end-of-life care is in its infancy, and, for the time being, is an unmet requirement (22-24). A previous study suggested that performance status and GPS, used together, act synergistically, thus improving the prognostic accuracy (19). Even if this was not entirely confirmed in the present study, patients with

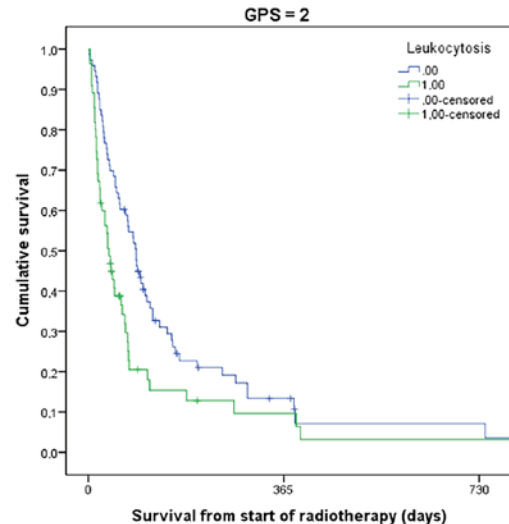


Figure 5. Actuarial overall survival following palliative radiotherapy in patients with GPS 2 stratified by leukocyte count [normal (n=73 patients) vs. increased (n=55 patients), P=0.007, log-rank test]. GPS, Glasgow prognostic score.

GPS 2 and ECOG PS 3 or 4 had short median survival rates. Possibly, the discrepancy between the two studies was caused by the small group sizes.

In the present study, it was established that it was possible to improve the prediction of short survival by combining leukocytosis and GPS 2. Patients with these two characteristics had a median survival of >6 weeks. This combination of variables has not been evaluated previously in the same setting.

Considering cancer-specific survival, Proctor *et al* (25) demonstrated that the prognostic value of the GPS improved by the addition of neutrophil and platelet counts and a high-sensitivity CRP measurement (>3 mg/l). Neither neutrophil counts nor high-sensitivity CRP assays were part of our standard work-up during the time period of the present study. In addition, the platelet count was not significantly associated with survival.

In conclusion, the present study has revealed that three widely available, inexpensive blood tests (CRP, albumin, and leukocyte count) provide clinically relevant prognostic information for radiation oncologists who decide upon fractionation. Further studies of the original GPS, and modified variants, are warranted.

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