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Palliative Radiotherapy in Cancer Patients with Increased Serum C-Reactive Protein Level

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Abstract. *Background/Aim: Connections exist between inflammation and cancer, for example with regard to disease progression and prognosis. Therefore, we investigated whether systemic inflammatory processes indicated by increased serum C-reactive protein (CRP) provide prognostic information for physicians prescribing palliative radiotherapy. Patients and Methods: We analyzed data from 781 patients and evaluated prognostic factors for survival. Results: Only 277 patients (35%) had CRP <8 mg/l before radiotherapy. No significant association was observed between CRP level and steroid treatment. In patients with the highest CRP level (>60 mg/l, 20% of patients), intravenous therapy with antibiotics was more common. CRP significantly influenced survival and contributed prognostic information together with established parameters, such as performance status (PS). In the multivariate model, white blood cell count did not provide relevant additional information. A simple four-tiered prognostic score solely based on CRP showed promising results. Conclusion: Most patients treated with palliative radiotherapy had increased CRP. This widely available biomarker might improve decision-making and should be further validated.*

The interplay between cancer and inflammation has long been of scientific interest (1, 2). Inflammatory biomarkers might provide prognostic information (3). Serum C-reactive protein (CRP) is a non-expensive widely available biomarker, which has been shown to predict survival for example in patients with localized and advanced colorectal cancer (4), liver metastases from colorectal cancer (5), metastatic prostate cancer (6), androgen-independent prostate cancer (7), urothelial bladder cancer (8), renal cell carcinoma (9) and pancreatic adenocarcinoma (10). These studies have also demonstrated correlations between CRP level and stage of disease or tumor load. In patients with cancer-related CRP increase, concomitant infection might complicate the picture because it also causes CRP increase. Patients with active infection might have to postpone their scheduled oncological treatment, *e.g.* chemo- or radiotherapy, because such treatment could cause immunosuppression and increase the risk of serious complications resulting, for example, in hospitalization and/or intensive care.

The use of palliative radiotherapy in patients with incurable cancer has increased during the last decades (11). Decision-making regarding radiotherapy indication and treatment schedule is not trivial. Prognostic scores and nomograms might be helpful. Despite the potential impact of CRP, this biomarker is not part of commonly used decision support models (12). Given that CRP measurement would not add significant cost to a course of palliative radiotherapy and would be affordable in many health care scenarios, its role should be investigated in large patient cohorts. Besides designing a study on CRP as prognostic factor in patients who received palliative radiotherapy, we were interested in the utilization of intravenous antibiotic treatment in patients with high CRP. We were also interested in utilization of steroids at the start of radiotherapy as these drugs have the potential to lower CRP levels (13) and, thereby, complicate analyses.

Patients and Methods

A retrospective analysis of the records of 781 consecutive patients with metastatic or otherwise incurable cancer who received palliative radiotherapy at a single institution and had available CRP measurement, was performed. Due to their different biological behavior, hematological and primary brain malignancies were not included. Radiotherapy was initiated during the time period from June 20, 2007 (date of opening of the institution's radiotherapy

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facility) to December 31, 2011. The treatment aim (curative/palliative) was defined by the treating physician at the time of assessment of a patient's referral documents. In general, palliative doses of radiotherapy are sufficient to achieve symptom improvement, but not definitive local tumor control. The typical workflow consisted of planning computed tomography (approximately one week before start of radiotherapy), physician consultation with assessment of the Eastern Cooperative Oncology Group (ECOG) performance status (PS) and blood tests the day before start of radiotherapy. However, individual variations existed. For this study, only blood test results obtained within one week before radiotherapy were accepted. Patients who took their blood tests outside of this time window were excluded (n=61). In case of multiple measurements during this time period, the most recent CRP level before radiotherapy was selected. The institutional limit of normal was <8 mg/l. Patients with abnormal CRP level were further stratified into different groups (<30, 30-60 and >60 mg/l). All medical records, treatment details and date of death were available 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. Survival time was measured from the first day of palliative radiotherapy. We used IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA) to evaluate the association between survival, CRP and other prognostic factors. Actuarial survival curves were generated by Kaplan-Meier method and compared by log-rank test. For multivariate analysis of survival, Cox regression analysis was used (forward stepwise method). All factors with 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 test. Statistical significance was defined as $p<0.05$ throughout this study in two-sided tests.

Results

Many different types of primary tumors were represented, with prostate cancer (26%), non-small cell lung cancer (NSCLC) (23%) and breast cancer (12%) accounting for the majority of all 781 cases. Common radiotherapy target volumes were spinal bone metastases (30%), pelvic bone metastases (18%), lung (14%) and brain (15%). Median actuarial survival was 159 days (5 months). A total of 277 patients (35%) had CRP <8 mg/l before radiotherapy. In 210 cases (27%), CRP was mildly increased (8-29 mg/l) and 137 patients (18%) had moderately increased CRP (30-60 mg/l). The remaining 157 patients (20%) had CRP >60 mg/l. Median age was 67.5-69 years in the four groups with different CRP levels (not significant). Median time from cancer diagnosis to radiotherapy was significantly longer in patients with normal CRP (39 months as compared to 19, 24 and 13 months in patients with increasingly pathological CRP, $p=0.0001$). As shown in Table I, univariate analysis revealed significant associations between CRP level and gender, ECOG PS, cancer type, number of target volumes (a surrogate of disease extent), hemoglobin level, white blood cell count (WBC), presence of hypercalcemia, presence of lung metastases, presence of adrenal gland metastases, pleural metastases and/or effusion, progressive disease outside of the radiotherapy target volume(s) and presence of comorbidity (specific comorbidities, such as diabetes or chronic obstructive pulmonary disease, all had *p*-values >0.05). There was no significant association between CRP and steroid utilization, $p=0.8$.

The number of prescribed radiotherapy sessions was significantly lower in patients with increasingly pathological CRP, $p=0.001$. For example, less than 10 fractions were prescribed in 31% of patients with normal CRP, as compared to 48%, 45% and 55% in the other 3 groups. Failure to complete the prescribed course of radiotherapy was significantly more common in patients with high CRP, $p=0.0001$ (2% if CRP was normal, 5% if CRP was 8-29 mg/l, 7% if CRP was 30-60 mg/l and 12% if CRP was >60 mg/l). The need for red blood cell transfusion during radiotherapy was significantly higher in patients with pathological CRP, $p=0.0001$ (1% if CRP was normal, 2% if CRP was 8-29 mg/l, 7% if CRP was 30-60 mg/l and 13% if CRP was >60 mg/l), as would be expected from the hemoglobin levels. Table II shows the use of intravenous antibiotics, which was significantly associated with CRP level, $p=0.0001$. Prescription of other antibiotics was not recorded in the EPR.

As shown in Figure 1, CRP significantly influenced survival. The one-year survival rates were 51%, 28%, 17% and 5%, respectively. We also performed an exploratory analysis comparing patients with CRP 60-90 mg/l and those with >90 mg/l. However, survival was not significantly different (median 66 *versus* 69 days, $p=0.18$, curves not shown). Furthermore, we analyzed the impact of CRP on survival in the subgroups of patients treated with and without steroids. Comparable differences in survival were seen in both subgroups (curves not shown). In patients with CRP >60 mg/l, stratification according to WBC provided little additional information (Figure 2). The same was true for those with CRP 30-60 mg/l (curves not shown). The multivariate Cox regression analysis included gender, time interval from diagnosis to radiotherapy, cancer type, all different sites of metastases, progressive disease outside of the radiotherapy target volume(s), ECOG PS, comorbidity, hypercalcemia, hemoglobin, WBC and CRP. Seven of these potential prognostic factors independently influenced survival: high CRP, poor ECOG PS, progressive disease, pleural metastases/effusion (all $p=0.0001$), short time interval ($p=0.009$), adrenal gland metastases ($p=0.01$) and high Charlson comorbidity index ($p=0.02$).

Median actuarial survival was 190 days in patients treated without intravenous antibiotics (Figure 3). Those who received such antibiotics during or before radiotherapy (within 2 weeks before start) had shorter median survival (63 and 75 days, respectively, $p=0.7$). The significance level was $p=0.0001$ for comparison between any antibiotic treatment

Table I. *Patients' characteristics and univariate analysis*.

Parameter	Normal CRP (n=277)	CRP 8-29 mg/l (n=210)	CRP 30-60 mg/l (n=137)	CRP>60 mg/l (n=157)	Significance level, *p*-Value
Female gender	108 (39%)	82 (39%)	34 (25%)	50 (32%)	
Male gender	169 (61%)	128 (61%)	102 (75%)	107 (68%)	0.02
ECOG PS 0-1	165 (60%)	84 (40%)	40 (29%)	27 (18%)	
ECOG PS 2	78 (28%)	77 (37%)	52 (38%)	51 (32%)	
ECOG PS 3-4	34 (12%)	49 (23%)	45 (33%)	79 (50%)	0.0001
Prostate cancer	97 (35%)	55 (26%)	29 (21%)	20 (13%)	
Breast cancer	47 (17%)	26 (12%)	10 (7%)	13 (8%)	
NSCLC	44 (16%)	46 (22%)	44 (32%)	49 (31%)	
SCLC	20 (7%)	16 (8%)	5 (4%)	6 (4%)	
Colorectal cancer	13 (5%)	13 (6%)	8 (6%)	15 (10%)	
Bladder cancer	8 (3%)	10 (5%)	9 (7%)	18 (11%)	
Kidney cancer	12 (4%)	16 (8%)	19 (14%)	14 (9%)	
Other cancer	36 (13%)	28 (13%)	13 (9%)	22 (14%)	0.0001
1 target volume	206 (74%)	135 (64%)	92 (67%)	86 (55%)	
>1 target volume	71 (26%)	75 (36%)	45 (33%)	71 (45%)	0.008
Normal hemoglobin	123 (44%)	140 (67%)	103 (75%)	136 (87%)	
Low hemoglobin	154 (56%)	70 (33%)	34 (25%)	21 (13%)	0.0001
Normal WBC	233 (84%)	151 (72%)	90 (66%)	83 (53%)	
Low WBC	9 (3%)	11 (5%)	2 (1%)	3 (2%)	
High WBC, no steroids	3 (1%)	8 (4%)	20 (15%)	34 (22%)	
High WBC, steroids	32 (12%)	40 (19%)	25 (18%)	37 (24%)	0.0001
Hypercalcemia	7 (3%)	10 (5%)	9 (7%)	15 (10%)	0.008
Brain metastases	65 (23%)	39 (19%)	25 (18%)	26 (17%)	0.25
Liver metastases	49 (18%)	47 (22%)	25 (18%)	43 (27%)	0.09
Lung metastases	52 (19%)	61 (29%)	37 (27%)	52 (33%)	0.006
Adrenal metastases	20 (7%)	24 (11%)	14 (10%)	28 (18%)	0.009
Bone metastases	179 (65%)	142 (68%)	99 (72%)	112 (71%)	0.35
Pleural metastases/effusion	20 (7%)	20 (10%)	18 (13%)	30 (19%)	0.01
Progressive disease[1]	120 (43%)	124 (59%)	85 (62%)	108 (69%)	0.0001
No comorbidity[2]	89 (32%)	46 (22%)	31 (23%)	31 (20%)	0.001
Steroids at start of RT	163 (59%)	118 (56%)	82 (60%)	88 (56%)	0.81
No systemic therapy before RT	113 (41%)	94 (45%)	68 (50%)	67 (43%)	0.38

CRP, C-Reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; WBC, white blood cell count; RT, radiotherapy. [1]Outside of the target volume(s). [2]Charlson comorbidity index 0 (not taking into account presently treated cancer).

Table II. *Univariate analysis of use of intravenous antibiotics*.

Parameter	Normal CRP (n=267)	CRP 8-29 mg/l (n=205)	CRP 30-60 mg/l (n=129)	CRP>60 mg/l (n=146)	Significance level, *p*
No antibiotics	254 (95%)	176 (86%)	106 (82%)	103 (70%)	
During RT	11 (4%)	22 (11%)	17 (13%)	33 (23%)	
Before RT (2 weeks)[1]	2 (1%)	7 (3%)	6 (5%)	10 (7%)	0.0001

CRP, C-Reactive protein; RT, radiotherapy. [1]Not consistently recorded in patients referred from other hospitals with own electronic patient records, available data in 747 patients.

and none. Regarding patients with the highest CRP levels, *i.e.* >60 mg/l, intravenous antibiotic treatment during radiotherapy did not on impact prognosis; however, a trend was seen for the small subgroup of 10 patients treated before radiotherapy who had very short survival (Figure 4). We reviewed the cause of death in these 10 patients. Only one died from infection (pneumonia). This patient had metastatic small cell lung cancer and the treatment aim was palliation of thoracic symptoms. All other patients died from rapid cancer progression.

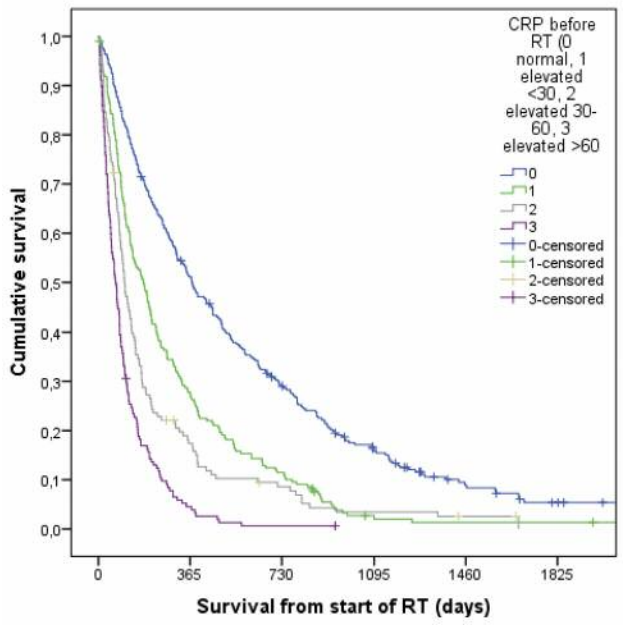

Figure 1. *Actuarial survival after palliative radiotherapy (RT); Kaplan-Meier analysis (median 373 days if C-reactive protein (CRP) <8 mg/l, 180 days if CRP 8-29 mg/l, 105 days if CRP 30-60 mg/l and 69 days if CRP >60 mg/l; p=0.01 for comparison between the two groups with CRP <8 mg/l and 8-29 mg/l, respectively; p=0.0001 for all other comparisons).*

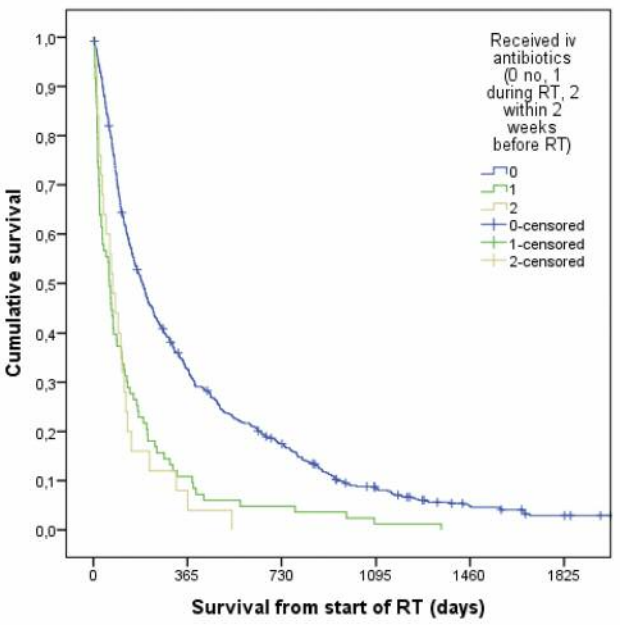

Figure 3. *Actuarial survival after palliative radiotherapy (RT) in patients with or without additional treatment with intravenous antibiotics; Kaplan-Meier analysis, p=0.0001 (0.7 for comparison between the two groups treated with antibiotics).*

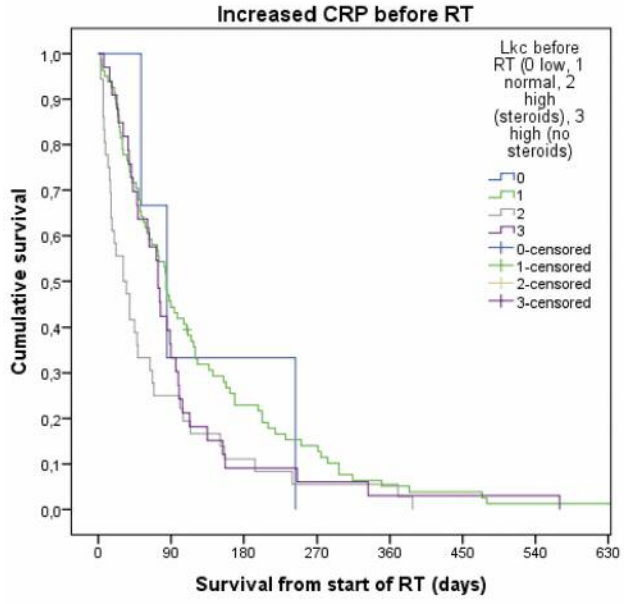

Figure 2. *Actuarial survival after palliative radiotherapy (RT) in patients with high C-reactive protein (CRP), i.e. >60 mg/l; Kaplan-Meier analysis stratified by white blood cell count (leukocytes (Lkc)), p>0.1.*

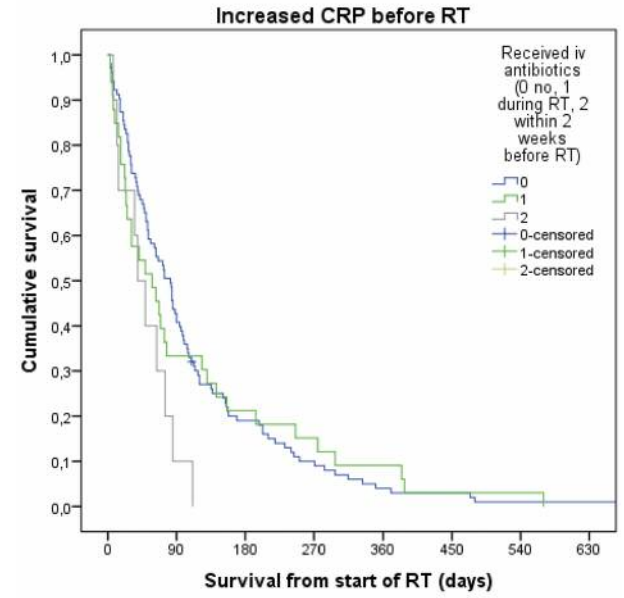

Figure 4. *Actuarial survival after palliative radiotherapy (RT) in patients with high C-reactive protein (CRP), i.e. >60 mg/l; Kaplan-Meier analysis stratified by intravenous antibiotics, p>0.1.*

Discussion

The present study is the first large-scale analysis of the potential role of CRP when estimating prognosis of patients referred to palliative radiotherapy. It has previously been shown that radiotherapy causes inflammation and increases CRP (14-16). Other studies suggested correlations between CRP and prognosis after curative radiotherapy, *e.g.* in prostate (17), rectal (18) and esophageal cancer (19). Such results are in line with those from studies of other treatment modalities and malignancies (6, 7, 9, 10, 20). The strengths of our study include the large number of patients (statistical power), long follow-up, consistency of pre-radiotherapy assessments, use of only one laboratory and assay for CRP measurement, as well as availability of information about several potential confounders, *e.g.* comorbidity, steroid medication, intravenous antibiotic therapy and WBC. Disadvantages include the retrospective design and lack of consistent documentation of oral antibiotics. We also acknowledge that a number of different individual physicians provided clinical care to our patients. Their attitude towards initiation of antibiotic therapy might have differed. A common challenge in clinical practice is to differentiate between pure cancer-related CRP increase and concomitant infection. Parameters such as fever, clinical symptoms, WBC, blood and urine culture might point towards infection and support decision-making. Likely, the threshold to start antibiotics was lower in patients with reduced PS, ongoing systemic therapy or other factors indicating that untreated infections could become life-threatening or compromise the oncological treatment plan. The timing of palliative radiotherapy in patients with recently treated infection might also differ. For example, patients with metastatic spinal cord compression might require immediate treatment, while patients with uncomplicated bone metastases can postpone radiotherapy and might have normal CRP before start. It is also important to be aware of the fact that CRP level might change from one day to another.

Our results showed limited impact of steroid medication on CRP level. This finding was unexpected and potentially related to the fact that many patients were in the terminal stage of their disease with known progression outside of the target volume(s) and no further systemic options. In this setting, the influence of steroids might become less pronounced. Certain cancer types and patterns of spread were associated with higher CRP levels, *e.g.* NSCLC, lung metastases and pleural affection. Patients with high CRP had higher likelihood of anemia, abnormal WBC and reduced PS. Especially, PS is a strong prognostic factor in all established models predicting survival after palliative radiotherapy (12). Our multivariate analysis suggested that CRP is not just a surrogate marker of reduced PS or other adverse prognostic factors. Rather CRP contributed important and complementary information. It would certainly be possible to develop a score that includes the other independent prognostic factors (PS, progressive disease outside of the target volume(s), pleural affection, short time interval from diagnosis to radiotherapy, adrenal gland metastases, comorbidity). However, as shown in Figure 1, CRP alone is sufficient to create a clinically useful 4-tiered score, which is readily available and easy to assess. No expensive analyses or imaging is needed, an important aspect in many countries with limited health care resources.

Use of intravenous antibiotics was not uncommon in patients with high CRP. This is understandable given the potential for serious complications of uncontrolled infection in patients receiving radiotherapy (many patients were elderly, with comorbidity and/or reduced PS). The retrospective design of our study is not adequate to better understand the necessity for antibiotics and their benefits and side-effects in the clinical setting of palliative radiotherapy. We were worried about the short survival of patients with CRP >60 mg/l who had received antibiotics during the two-week time period before radiotherapy (Figure 4). Aggravation or relapse of infection promoted by inappropriately early radiotherapy could be a potential explanation for short survival. However, only one patient (10%) in this small subgroup actually died from uncontrolled infection. Rapid cancer progression was the prevailing cause of death. Most likely these patients had cancer-related CRP increase and the clinicians decided to terminate the antibiotics after a trial period where CRP did not decrease. The complicated issue of optimal utilization of antibiotics in patients with incurable cancer requires prospective studies.

In conclusion, our data provide a strong impetus for further research about CRP and inflammatory markers in general in patients who receive palliative radiotherapy. Even larger databases than ours are needed to optimize and validate our prognostic score, which was based on arbitrarily defined levels of mildly and moderately increased CRP. Biomarkers might improve current prognostic models and facilitate individualized cancer treatment, *e.g.* in the context of too aggressive or lengthy treatment schedules in poor prognosis patients or near the end of life.

References

1 Baskic D, Popovic S, Bankovic D, Arsovic A, Vukovic V, Zelen I and Djurdjevic P: Evaluation of inflammatory biomarkers as helping diagnostic tool in patients with breast cancer. Cancer Biomark *14*: 401-408, 2014. doi: 10.3233/CBM-140426

2 Chiorean R, Berindan-Neagoe I, Braicu C, Florian IS, Leucuta D, Crisan D and Cernea V: Quantitative expression of serum biomarkers involved in angiogenesis and inflammation, in patients with glioblastoma multiforme: correlations with clinical data. Cancer Biomark *14*: 185-194, 2014. doi: 10.3233/CBM-130310

3 Liao C, Yu Z, Guo W, Liu Q, Wu Y, Li Y and Bai L: Prognostic value of circulating inflammatory factors in non-small cell lung cancer: A systematic review and meta-analysis. Cancer Biomark *14*: 469-481, 2014. doi: 10.3233/CBM-140423

4 Pathak S, Nunes QM, Daniels IR and Smart NJ: Is C-reactive protein useful in prognostication for colorectal cancer? A systematic review. Colorectal Dis *16*: 769-776, 2014. doi: 10.1111/codi.12700

5 Hamilton TD, Leugner D, Kopciuk K, Dixon E, Sutherland FR and Bathe OF: Identification of prognostic inflammatory factors in colorectal liver metastases. BMC Cancer *14*: 542, 2014. doi: 10.1186/1471-2407-14-542

6 Xu L, Zhao Q, Huang S, Li S, Wang J and Li Q: Serum C-reactive protein acted as a prognostic biomarker for overall survival in metastatic prostate cancer patients. Tumour Biol *36*: 669-673, 2015. doi: 10.1007/s13277-014-2670-x

7 Beer TM, Lalani AS, Lee S, Mori M, Eilers KM, Curd JG, Henner WD, Ryan CW, Venner P, Ruether JD and Chi KN, ASCENT Investigators: C-reactive protein as a prognostic marker for men with androgen-independent prostate cancer: results from the ASCENT trial. Cancer *112*: 2377-2383, 2008.

8 Masson-Lecomte A, Rava M, Real FX, Hartmann A, Allory Y and Malats N: Inflammatory biomarkers and bladder cancer prognosis: A systematic review. Eur Urol *66*: 1078-1091, 2014.

9 Hu Q, Gou Y, Sun C, Ding W, Xu K, Gu B, Xia G and Ding Q: The prognostic value of C-reactive protein in renal cell carcinoma: a systematic review and meta-analysis. Urol Oncol *32*: 50.e1-8, 2014.

10 Szkandera J, Stotz M, Absenger G, Stojakovic T, Samonigg H, Kornprat P, Schaberl-Moser R, Alzoughbi W, Lackner C, Ress AL, Seggewies FS, Gerger A, Hoefler G and Pichler M: Validation of C-reactive protein levels as a prognostic indicator for survival in a large cohort of pancreatic cancer patients. Br J Cancer *110*: 183-188, 2014.

11 Nieder C, Pawinski A, Haukland E, Dokmo R, Phillipi I and Dalhaug A: Estimating need for palliative external beam radiotherapy in adult cancer patients, Int J Radiat Oncol Biol Phys *76*: 207-211, 2010.

12 Nieder C and Gaspar LE (eds.) Decision tools for radiation oncology. Springer 2014.

13 Brotman DJ, Girod JP, Garcia MJ, Patel JV, Gupta M, Posch A, Saunders S, Lip GY, Worley S and Reddy S: Effects of short-term glucocorticoids on cardiovascular biomarkers. J Clin Endocrinol Metab *90*: 3202-3208, 2005.

14 Schaue D, Micewicz ED, Ratikan JA, Xie MW, Cheng G and McBride WH: Radiation and inflammation. Semin Radiat Oncol *25*: 4-10, 2015.

15 Tolia MG, Kouloulias VE, Pantelakos PS and Syrigos KN: Changes of acute-phase protein levels in the serum of lung cancer patients following radiotherapy. Int J Clin Exp Med *6*: 50-56, 2013.

16 Ehrsson YT, Hellström PM, Brismar K, Sharp L, Langius-Eklöf A and Laurell G: Explorative study on the predictive value of systematic inflammatory and metabolic markers on weight loss in head and neck cancer patients undergoing radiotherapy. Support Care Cancer *18*: 1385-1391, 2010.

17 Hall WA, Nickleach DC, Master VA, Prabhu RS, Rossi PJ, Godette K, Cooper S and Jani AB: The association between C-reactive protein (CRP) level and biochemical failure-free survival in patients after radiation therapy for nonmetastatic adenocarcinoma of the prostate. Cancer *119*: 3272-3279, 2013.

18 Toiyama Y, Inoue Y, Saigusa S, Kawamura M, Kawamoto A, Okugawa Y, Hiro J, Tanaka K, Mohri Y and Kusunoki M: C-reactive protein as predictor of recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. Anticancer Res *33*: 5065-5074, 2013.

19 Wang CY, Hsieh MJ, Chiu YC, Li SH, Huang HW, Fang FM and Huang YJ: Higher serum C-reactive protein concentration and hypoalbuminemia are poor prognostic indicators in patients with esophageal cancer undergoing radiotherapy. Radiother Oncol *92*: 270-275, 2009.

20 Kim YJ, Kim SJ, Lee JK, Choi WS, Park JH, Kim HJ, Sim SH, Lee KW, Lee SH, Kim JH, Kim DW, Lee JS, Bang YJ and Heo DS: Prediction of survival in terminally ill cancer patients at the time of terminal cancer diagnosis. J Cancer Res Clin Oncol *140*: 1567-1574, 2014.

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