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Abstract: Renal function impairment in lung cancer patients with bone metastases was investigated, as this can limit the application of bisphosphonates representing the gold standard in the management of such cases. Clinicopathological data of 570 lung cancer patients were retrospectively analysed for changes in renal function parameters. Co-morbidities included hypertension (50%), COPD (33%) and diabetes mellitus (15%). Statistical analysis was performed with Fisher's exact tests and a Cox proportional hazards model. In patients suffering from hypertension, both median serum creatinine and blood urea nitrogen (BUN) were higher (81.9 *versus* 75.8 µmol/l, p<0.001 and 6.0 *versus* 5.7 mmol/l, p=0.005, respectively). Such a difference could not be observed in patients with diabetes. In COPD patients, only serum creatinine was higher (81.1 *versus* 77.3 µmol/l, p=0.004). In the whole cohort, we found that while at the time of lung cancer diagnosis the ratio of patients in the pathological range (PRR) was 8.67% for serum creatinine (median: 75 µmol/l) and 14.16% for BUN (median: 5.4 mmol/l), at the time of bone metastasis the PRR for serum creatinine increased to 16.11% (median: 77.0 µmol/l) and for BUN to 24.07% (median: 6.0 mmol/l), which is a significant increase for both parameters (p<0.001). For the whole cohort, the last laboratory results showed a 26.37% PRR for serum creatinine and 45.66% PRR for BUN (significant increase for both, p<0.001). Multivariate analysis revealed that patients with hypertension had a higher chance for switching to the pathological range sooner (p=0.033, HR: 1.372, CI: 1.025-1.835). Also, the appearance of the bone metastasis correlated with an acceleration of the onset of such a switch (p<0.001, HR: 2.655, CI: 1.581-4.456). Our results suggest that renal function is impaired in a significant proportion of lung cancer patients and highlight the importance of non-nephrotoxic drug in the management of bone metastases.

Keywords:

Lung cancer, bone metastasis, renal function, bisphosphonate treatment

Abbreviations:

ADC: adenocarcinoma

BS: survival after bone metastasis

BUN: blood urea nitrogen

COPD: chronic obstructive pulmonary disease

CT: computed tomography

EGFR-TKI: epidermal growth factor receptor – tyrosine kinase inhibitor

FR: failure rate; ratio of new pathological cases for a time period

MRI: magnetic resonance imaging

NSCLC: non-small cell lung cancer

OS: overall survival

PET: positron emission tomography

PRR: ratio of cases with laboratory data in the pathological range

SCC: squamous cell carcinoma

SCLC: small cell lung cancer

Lung cancer is the leading cause of cancer mortality worldwide. 25-30% of lung cancer patients present with skeletal involvement at the time of diagnosis of primary tumour and another 10% of patients develop bone metastasis during disease progression [1]. As lung cancer is the most common cancer in the world with 1.8 million new cases diagnosed in 2012, the expected incidence of lung cancer with bone metastasis is around 600,000-700,000 worldwide [2].

Bone metastases in lung cancer are associated with significant morbidity, loss of functional independence and reduction in quality of life [3]. Patients who developed a skeletal-related event (SRE) have a prognosis worse than patients without SRE: this occurrence increases the risk of death by 20% to 40% [4]. Prevention of SREs in lung cancer could have an important economic impact demonstrated in a study of Delea *et al*. as the increased healthcare cost in patients with SREs was estimated at approximately 27,982 USD, while the cost of treatment of SREs was 9480 USD per patient [5,6].

Bisphosphonates, specific inhibitors of osteoclasts, have an important role in the treatment of tumour-induced hypercalcaemia and in decreasing the frequency of SREs. Recently, it has been proposed that these agents may prevent skeletal metastases [7]. Among bisphosphonates, zoledronic acid is the most commonly used drug to prevent, reduce the incidence and delay the onset of SREs. However, avoidance of use of these drugs is recommended in patients with renal impairment, and consideration should be given to using drugs that do not require dose adjustment based on glomerular filtration rate [8,9,10].

The relationship of renal function and cancer has been described in a number of publications, as Malyszko has summarized in a recent review with 169 references [11]. This publication gives an excellent overview of chronic kidney disease in different malignancies, however, it refers only to a single article about lung cancer, in which renal insufficiency and anti-cancer medication were analysed in 445 patients [12]. They found that 14.4% of patients had a serum creatinine level >110 μmol/L, however, when they were assessed using the Cockcroft–Gault formula, 62.1% had abnormal renal function.

Lung cancer mainly occurs in elderly people as about 2 out of 3 people diagnosed with lung cancer are 65 years or older [13]. It has been estimated that active smoking is responsible for close to 90% of lung cancer cases. Both the advanced age, as well as the cardiovascular disorders caused by smoking increase the risk of renal impairment. In addition, platinum-based chemotherapy used as first line treatment in lung cancer is also nephrotoxic. Despite all this, we have little information about the renal function of either lung cancer patients or lung cancer patients with bone metastases. Kutluk *et al.* studied 298 stage IV non-small cell lung cancer patients and found that renal function fell below commonly used thresholds for cisplatin and for pemetrexed in fewer than a quarter of patients [14]. They, however, did not analyse the changes in renal function during the progression of lung cancer, nor stratified patients according to the site of distant metastasis.

The aim of the present study was to retrospectively analyse the clinicopathological data of lung cancer patients with bone metastasis to estimate the proportion of patients in whom bisphosphonate treatment is hampered by decreased renal function. Our main goal was to determine the influencing factors of the renal function deterioration, including co-morbidities, previously administered platinum-based cytotoxic chemotherapy, and the malignant process itself.

Materials and methods

Patient data

We analysed the clinicopathological data of 570 lung cancer patients with bone metastasis, including unselected 405 consecutive patients with proven bone metastasis and 165 selected patients with previous surgical resection of the primary tumour. Ethical permission for the study was granted by the Scientific and Research Ethics Committee of the Medical Research Council (ETT-TUKEB No 510/2013 and No 109/2016).

Bone metastasis, treatments and co-morbidities

At the time of lung cancer diagnosis, 196 patients suffered from bone metastasis, and others developed bone involvement during disease progression.

The diagnosis of bone metastasis was established in all cases by imaging procedures, including Technetium-99m (^{99m}Tc) bone scintigraphy, CT scanning, magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning or conventional radiography.

Beside surgical resection of the primary tumor, other types of active oncotherapy, including chemotherapy, molecular targeted treatment and bisphosphonate treatment were also analysed.

The most important co-morbidities that might influence the renal function of patients, including diabetes mellitus, hypertension and COPD were also recorded. The clinical, histopathological and radiological data for all cases are summarized in Table 1.

Investigated renal function parameters

We have recorded the level of serum creatinine and BUN at the time of both the diagnosis of lung cancer and the diagnosis of bone metastasis. Ranges between 36-106 μmol/l for serum creatinine and 1.7-8.3 mmol/l for BUN were considered normal. Patients with postoperative complications, such as acute infection or sepsis which could have influenced the laboratory results were excluded from this analysis. Regarding the creatinine and BUN levels, the results before death or the last available laboratory results were also recorded.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5 software (GraphPad Software Inc., San Diego, USA) for Mann-Whitney U test and Spearman non-parametric correlation, while SPSS 17.0 software (SPSS Inc., Chicago, Ill, USA) was used for multiple regression survival analysis. We confronted the other variables with Fisher's exact tests. A Cox proportional hazard model was applied (R survival package) for the analysis of the switching time to the pathological range. We considered $p<0.05$ as a statistically significant difference.

Results

Time to bone metastasis, overall survival (OS) and survival from bone metastasis (BS)

The median time to bone metastasis was 4.20 months (0-150 months). There were differences between patients with surgically resected primary tumour and patients without surgery in favour of the operated group (61.0 *versus* 4.4 weeks, p<0.001, Mann-Whitney).

The median OS was 13.7 months. Primary tumour resection, performed in 189 patients, favourably influenced OS (10.1 *versus* 29.8 months, p<0.001, Mann-Whitney).

Chemotherapy applied only before bone metastasis increased OS (17.4 *versus* 13.5 months, p=0.025, Mann-Whitney), however, it did not influence BS. Chemotherapy applied only after skeletal involvement resulted in better BS (9.4 *versus* 3.2 months, p<0.001, Mann-Whitney). In patients who received chemotherapy both before and after bone metastasis, no significant OS benefit could be demonstrated (p=0.27, Mann-Whitney), but BS was longer (7.4 *versus* 3.9 months, p<0.001, Mann-Whitney).

Bisphosphonate therapy after bone metastasis diagnosis resulted only in a tendency of better OS (14.8 *versus* 9.2 months, p=0.074, Mann-Whitney). BS, however, was significantly better in these patients (7.5 *versus* 2.1 months, p<0.001, Mann-Whitney).

Serum creatinine level at the time of lung cancer diagnosis did not have a clear relation with OS, however, in case of increased BUN shorter OS could be observed (7.4 *versus* 14.5 months, p=0.044, Mann-Whitney). Similarly, serum creatinine level at the time of bone metastasis diagnosis did not have a connection with BS, however, a tendency between increased BUN and shorter BS could be demonstrated (6.8 *versus* 3.0 months, p<0.001, Mann-Whitney).

Renal function parameters at the time of lung cancer diagnosis

There was a correlation between older age and higher renal function parameters at the time of lung cancer diagnosis (p<0.001, R=0.225 Spearman) for both parameters. In cases with abnormal creatinine level, the mean age was 64.4 *versus* 61.8 years in the normal range (p=0.060, Mann-Whitney). Similarly, in cases with abnormal BUN level, the mean age was 67.1 years, whereas in the normal range, it was 61.2 years (p<0.001, Mann-Whitney).

Renal function parameters were higher in men at the time of lung cancer diagnosis (median creatinine: 83.4 *versus* 71.6 µmol/l, p<0.001 and median BUN: 6.1 *versus* 5.5 mmol/l, p<0.001, respectively, Mann-Whitney). Increased serum creatinine was observed in 10.2% of men and in 5.1% of women, whereas BUN was increased in 15.9% of men and 8.9% of women.

Interestingly, we found no correlation between smoking and renal function parameter levels either in the never/ever smoker, or in the never/ex-/current smoker categories.

To investigate the relationship between co-morbidities and renal function parameters at the time of lung cancer diagnosis, the ratio of patients with parameters in the pathological range (PRR = "pathological range ratio") for each co-morbidity group and renal function parameter was calculated (Table 2). Table 2 indicates that using 8 different co-morbidity groups for statistical analysis is impractical due to the relatively small number of cases in some of them.

To determine which co-morbidities seem to influence renal function parameters the most, median values were compared for cases with and without a single co-morbidity. In patients suffering from hypertension, both median serum creatinine and BUN were higher (81.9 *versus* 75.8 µmol/l, $p<0.001$ and 6.0 *versus* 5.7 mmol/l, $p=0.005$, respectively, Mann-Whitney). Such a difference could not be observed in patients with diabetes. In COPD patients, only serum creatinine was higher (81.1 *versus* 77.3 µmol/l, $p=0.004$, Mann-Whitney).

As the presence of hypertension seems to separate patients with high *versus* low renal function parameters the most efficiently out of all investigated co-morbidities, , further analyses were performed using two co-morbidity groups, defined as patients who suffer from hypertension and patients who do not. For different features of the analysis, see Fig. 1.

In the case of serum creatinine levels, patients without hypertension have a lower PRR at diagnosis than patients with hypertension (Fig. 1A). This is supported by a borderline significant p-value of 0.053 (Fisher's exact; Supplementary file 1, Table S1.1). The same tendency for BUN levels could be observed (Fig. 1D) but not verified with a significance test. At this point, neither chemotherapy nor bisphosphonate treatment should have any effect on PRR, as neither was administered to any of the patients at the time of lung cancer diagnosis. Thus, any differences that could be seen in the initial PRR values for different treatment groups would be due to the fact that during treatment selection the values of laboratory parameters are taken into account.

Changes in renal function parameters from diagnosis to bone metastasis

We define the failure rate (FR) of a group for a given time period as the ratio of patients who have renal function parameters in the normal range in the beginning of the time period, but who switch to the pathological range by the end of it and the size of the group. In other words, FR is the ratio of new pathological cases in the group.

In the whole cohort, we found that while at the time of lung cancer diagnosis the PRR was 8.67% for serum creatinine (median: 75 µmol/l) and 14.16% for BUN (median: 5.4 mmol/l), at the time of the bone metastasis the PRR for serum creatinine increased to a 16.11% value

(median: 77.0 µmol/l) and for BUN to 24.07% (median: 6.0 mmol/l). This is a significant increase in median values for both parameters ($p<0.001$, Mann-Whitney).

Comparing patients with and without hypertension (Fig. 1B and 1E) resulted in significantly higher FRs for both serum creatinine and BUN in the group of patients with hypertension ($p=0.010$ and $p=0.005$, respectively, Fisher's exact, Supplementary file 1, Table S1.2), meaning that patients who suffer from hypertension are significantly more likely to switch to the pathological range from an initially normal value by the time of the bone metastasis than patients without hypertension. To assess the relationship of chemotherapy before bone metastasis and FR, co-morbidity groups of hypertension *versus* no hypertension were further grouped into treatment groups of chemotherapy *versus* no chemotherapy. We found that in both co-morbidity groups, patients who received chemotherapy before the bone metastasis had higher FRs than patients who did not, thus were more likely to switch to the pathological range for both serum creatinine and BUN. A significant difference was only established in the case of "no hypertension + chemotherapy *versus* no hypertension + no chemotherapy" comparison for serum creatinine ($p=0.006$, Fisher's exact), but strong tendencies to this effect could be observed in all other comparisons (Supplementary file 1, Table S1.3).

Changes in renal function parameters from bone metastasis to the last laboratory results

For the whole cohort, the last laboratory results showed a 26.37% PRR for serum creatinine (median: 83 µmol/l) and 45.66% PRR for BUN (median: 7.60 mmol/l), which is a significant increase from the median values measured at the bone metastasis ($p<0.001$ for both, Mann-Whitney).

After the bone metastasis, FRs of patients with and without hypertension are not significantly different from each other (Fig. 1C and 1F), but significantly higher than before the bone metastasis (Fig. 1B and 1D) for patients without hypertension for both serum creatinine and BUN ($p=0.010$ and $p<0.001$, respectively, Fisher's exact test) and BUN for patients with hypertension ($p=0.025$, Fisher's exact test; Supplementary file 1, Table S1.4).

After bone metastasis, the majority of the patients received bisphosphonate treatment, which can explain the significantly increased FRs in this group (Supplementary file 1, Table S1.5). In patients who did not receive bisphosphonate treatment, FR was also slightly increased in most cases, and a significant increment was found in patients with hypertension for serum creatinine ($p=0.042$, Fisher's exact test; Supplementary file 1, Table S1.5). The latter result suggests that the deterioration of serum creatinine levels after the bone metastasis is accelerated but not solely due to the effects of bisphosphonate treatment.

We also found that chemotherapy after the bone metastasis is accompanied by a significant increase in FRs (Supplementary file 1, Table S1.6).

Multivariate model for the time of switching to the pathological range

To find significant prognostic factors of the time it takes for a patient with normal renal function parameters to switch to the pathological range, a multivariate Cox-model was built using actual times instead of the above-described abstract time steps (at lung cancer diagnosis, at bone metastasis, last laboratory). The details of model building and the approach for model selection can be found in Supplementary file 2.

The most interesting results for serum creatinine were that patients with hypertension were more likely to switch to the pathological range sooner ($p=0.020$, HR: 1.639, CI: 1.081-2.485) and switches after the bone metastasis occurred significantly sooner than before the bone metastasis ($p<0.001$, HR: 3.022, CI: 1.591-5.740), suggesting that the appearance of the bone metastasis itself accelerates the increase in serum creatinine levels. Other relevant factors are presented in Supplementary file 2.

Similarly for BUN, patients with hypertension have a higher chance for switching to the pathological range sooner ($p=0.033$, HR: 1.372, CI: 1.025-1.835). Also, the appearance of the bone metastasis seemed to accelerate the onset of such a switch ($p<0.001$, HR: 2.655, CI: 1.581-4.456). Other relevant factors are presented in Supplementary file 2.

To more clearly illustrate that the appearance of bone metastasis has a significant effect on renal function independently on the treatment received, Kaplan-Meier curves were plotted for patients who did not receive either bisphosphonate treatment or chemotherapy for their bone metastasis (Fig. 2).

Discussion

We analysed data of lung cancer patients in a case-by-case manner in order to avoid bias of population-based data. Our results highlight the importance of co-morbidities in lung cancer patients with bone metastasis as we found that in the late phase of the disease, 27% of patients had abnormal creatinine level, and 46% of patients had abnormal BUN level due to co-morbidities affecting the kidney, applied oncotherapies and seemingly the appearance of bone metastasis. Apart from EGFR-TKI treatment in patients with advanced stage lung adenocarcinoma with sensitizing EGFR mutation, which is a minority of lung cancer patients, platinum-based chemotherapy is the gold standard of oncotherapy in surgically unresectable cases [15]. Application of this treatment, however, is often limited by poor kidney function [16]. Moreover, in case of bone metastasis, which occurs in up to 40% of lung cancer cases, the necessary bisphosphonate treatment is also limited by impaired renal function [17]. Approximately 90% of lung cancer cases are attributed to cigarette smoking, which is also responsible for other morbidities, such as hypertension and diabetes both of which have been known to contribute to the deterioration of renal function. Our data are in line with

the findings of Edwards *et al.*, who reported that lung cancer had the highest prevalence of co-morbidities compared with colorectal, breast or prostate cancers [18].

At the time of lung cancer diagnosis, we found impaired kidney function determined by abnormal creatinine level in 8% of patients. This proportion is somewhat higher than that found in a recent large study of 5683 lung cancer patients, in which renal disease was recorded in 5.7% of patients [19]. This might be explained by the fact that we investigated lung cancer patients with bone metastasis which was already present at the time of diagnosis in 40% of the patients. Bone metastasis is known to impair kidney function as it has already been demonstrated in a large cohort of 15,623 cancer patients including 3,839 patients with bone metastasis [20]. This is in line with our results which showed that the appearance of bone metastasis has a significant effect on renal function and was independent on the bisphosphonate treatment and/or chemotherapy received. Our study analysed renal function not only at the time of lung cancer diagnosis but also at the time of bone metastasis diagnosis as well as used the last available laboratory data. This approach gave us the possibility to demonstrate the deterioration of renal function in a longitudinal way, as it has never been studied before. Furthermore, to the best of our knowledge, our study group is the largest and most homogeneous cohort of lung cancer patients regarding the site of distant metastasis with such kidney function results.

The weakness of our study, however, is that we analysed serum creatinine and BUN used in the routine clinical practice instead of glomerular filtration rate. Estimated glomerular filtration rate was found to be a more sensitive indicator of renal impairment; therefore, our results certainly underestimate the proportion of patients with decreased kidney function [12,20]. In this light, our results further raise awareness that in this patient population, application of nephrotoxic drugs may frequently require dose adjustment or discontinuation.

Bisphosphonates are potent drugs used to inhibit osteoclast-mediated bone resorption and prevent SREs. In pre-clinical studies on human cancer cells lines derived from both SCLC and NSCLC, they seem to inhibit proliferation, induce apoptosis and have an immunomodulatory effect and active anti-tumour immune response [21-23]. Furthermore, recently, adjuvant bisphosphonate therapy was found to reduce the rate of bone metastasis development and improve breast cancer survival in women who were postmenopausal when treatment began [24]. Because of this, our findings highlight the importance of renal function control before bisphosphonate treatment not only in lung cancer patients with bone metastasis but also in breast cancer patients in whom bisphosphonates are intended to be used for prevention of distant metastases.

In summary, our results demonstrate that renal function is impaired in a significant proportion of lung cancer patients and hypertension is an important co-morbidity, which facilitates its development. These findings highlight the importance of considering the application of non-nephrotoxic drugs in the management of lung cancer patients with bone metastases and impaired renal function [25].

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Conflict of interest

The authors declare no known conflicts of interest associated with this publication.

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Tables

	Number	Age (years)
Patients	570	61.95 (33-89)
Male	335	62.04 (37-89)
Female	235	61.82 (33-89)
Histology		
Adenocarcinoma	321	
Squamous cell carcinoma	129	
Small cell lung cancer	61	
Anaplastic carcinoma	41	
Adenosquamous carcinoma	11	
Large cell carcinoma	7	
Stages at the time of lung cancer diagnosis (available in 555 cases)		
I	67	
II	52	
IIIA	97	
IIIB	46	
IV	293	
Bone metastasis	196	
Bone metastasis	total: 631∗	
^{99m}Tc bone scintigraphy	243	
Computed tomography (CT)	167	
Magnetic resonance imaging (MRI)	62	
Positron emission tomography (PET)	45	
Conventional radiography	114	
Active oncotherapy		
Primary lung cancer surgery	189	
Chemotherapy	236	
EGFR-TKI	17	
EGFR-TKI + chemotherapy	9	
Bisphosphonate treatment	438	
zoledronic acid	148	
pamidronat	69	
clodronat	166	
lodronat	23	
bisphosphonate not specified	32	
Co-morbidities		
Hypertension	284	
Diabetes mellitus	86	
COPD	189	

Table 1. Clinicopathological characteristics of lung cancer patients with bone metastasis

∗: In 61 cases, two different imaging techniques provided the diagnosis of bone metastasis

Co-morbidities	Serum creatinine	BUN	Number of cases
no co-morbidity	7.78%	15.56%	180
only hypertension	11.81%	11.81%	144
only diabetes	8.33%	25.00%	12
only COPD	2.38%	7.14%	84
hypertension + diabetes	12.20%	17.07%	41
hypertension + COPD	8.33%	14.29%	72
diabetes + COPD	14.29%	14.29%	7
all co-morbidities	12.00%	16.00%	25

Table 2. Ratio of patients in the pathological range (PRR) for serum creatinine and BUN for different co-morbidity groups at the time of lung cancer diagnosis (number of cases included)

The "number of cases" column contains the number of patients in each group where renal function parameters are available.

	All patients	Males	Females	p-value
Serum creatinine (median)				
At the time of lung cancer diagnosis	75.0 µmol/l	81.0 µmol/l	68.0 µmol/l	p<0.001
At the time of bone metastasis diagnosis	77.0 µmol/l	81.0 µmol/l	70.0 µmol/l	p<0.001
Last available data	83.0 µmol/l	87.0 µmol/l	79.0 µmol/l	p=0.001
Blood urea nitrogen (BUN) (median)				
At the time of lung cancer diagnosis	5.4 mmol/l	5.7 mmol/l	5.2 mmol/l	p=0.001
At the time of metastasis bone diagnosis	6.0 mmol/l	6.4 mmol/l	5.7 mmol/l	p=0.005
Last available data	7.6 mmol/l	8.2 mmol/l	7.1 mmol/l	p=0.005

Table 3. Laboratory parameters in lung cancer patients with bone metastasis (p-values indicate results of the Mann-Whitney U test for median comparison)

Figure titles and legends

Figure 1.

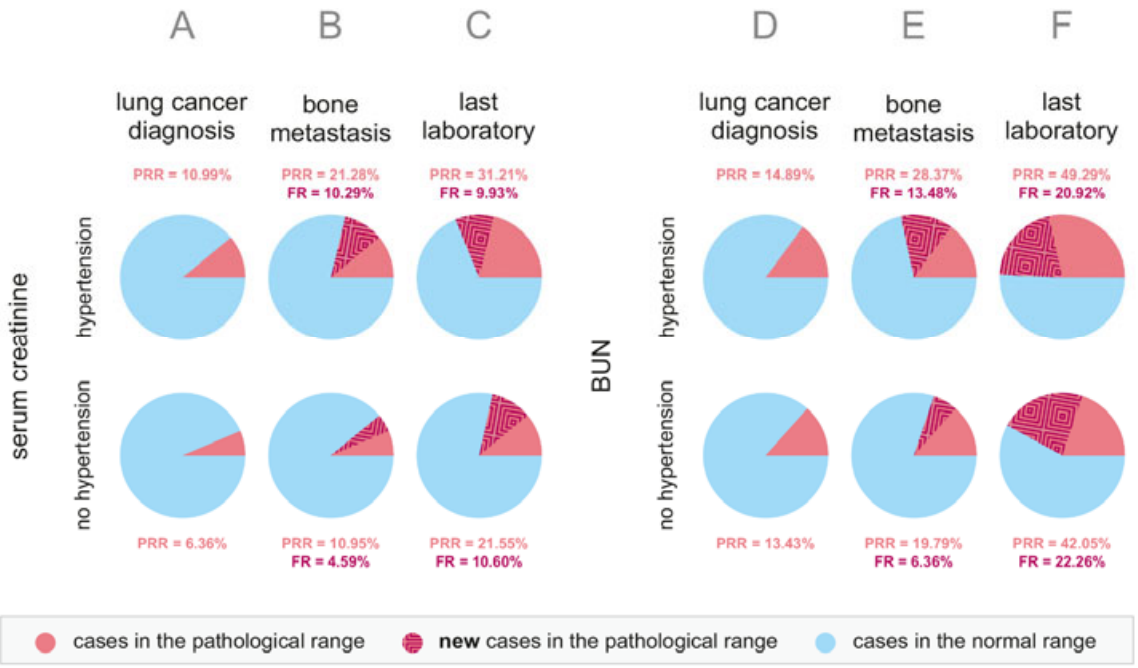

Figure 1. Changes in the ratio of cases in the pathological range (PRR) during the course of the disease.

(A) Differences between initial values of PRR for serum creatinine between patient groups of hypertension *versus* no hypertension. (B) Differences of PRR and FR values for serum creatinine at the time of the bone metastasis. FR (failure rate) values represent the ratio of new pathological cases in the group (indicated with the patterned area), while PRR values depict the ratio of the total number of pathological cases in the group. (C) Differences of PRR and FR values for serum creatinine at the time of the last laboratory results. (D) Differences of initial values of PRR for BUN between patient groups of hypertension *versus* no hypertension. (E) Differences of PRR and FR values for BUN at the time of bone metastasis. (F) Differences of PRR and FR values for BUN at the time of the last laboratory results.

Figure 2.

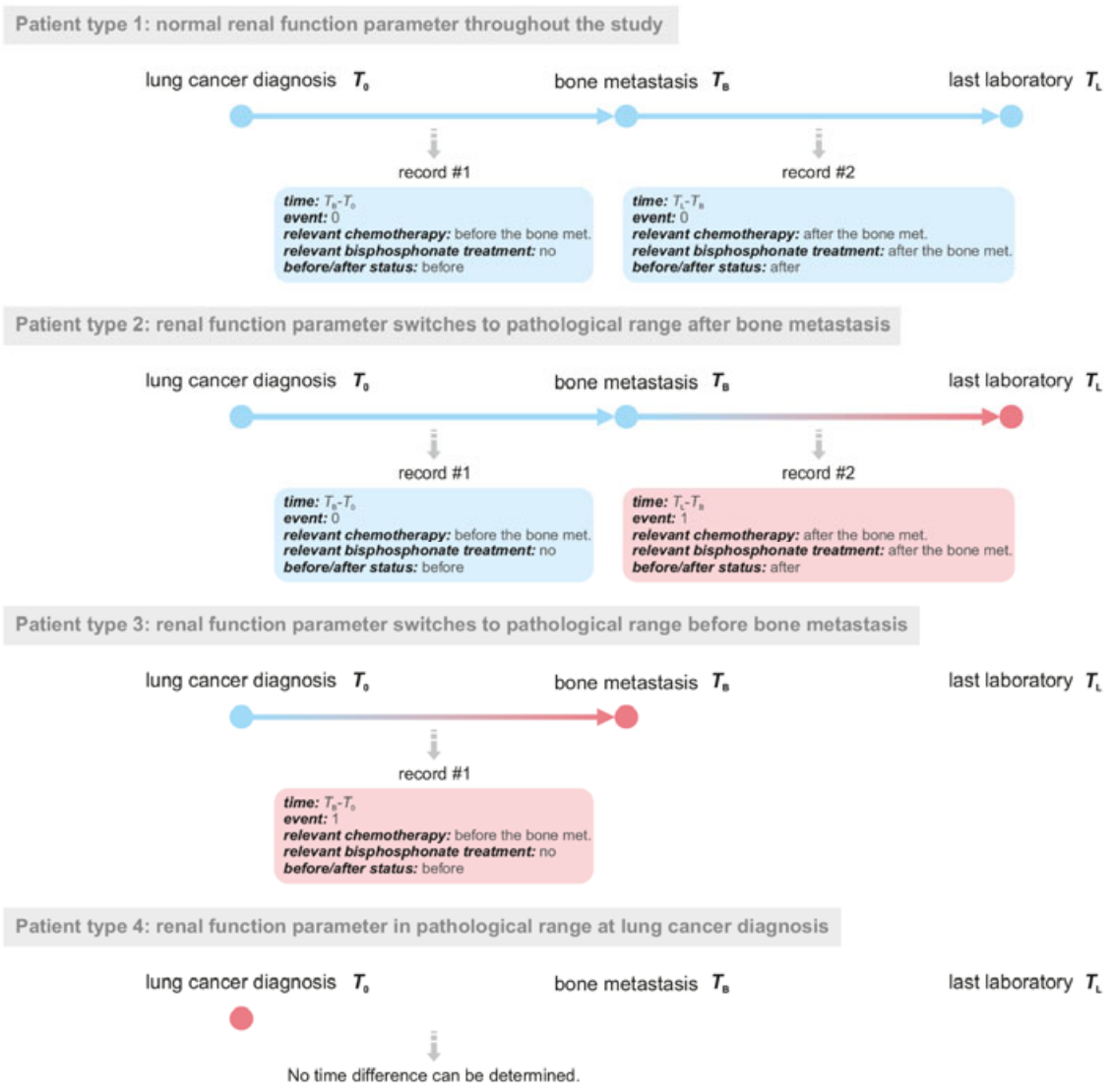

Figure 2. Kaplan-Meier curves for patients who did not receive bisphosphonate and/or chemotherapy.

References

S2. Collett D. Modelling Survival Data in Medical Research. London: Chapman & Hall; 1994.