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Osteosarcoma follow-up: chest X-ray or computed tomography?

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Abstract

Background: In patients with relapsed osteosarcoma, the surgical excision of all metastases, defined as second complete remission (CR-2), is the factor that mainly influences post-relapse survival (PRS). Currently a validated follow-up policy for osteosarcoma is not available, both chest X-ray and computed tomography (CT) are suggested for lung surveillance. The purpose of this study is to evaluate whether the type of imaging technique used for chest surveillance, chest X-ray or CT, influenced the rate of CR-2 and prognosis in patients with recurrent osteosarcoma.

BACKGROUND

- High-grade osteosarcoma is the most frequent primary bone tumor with almost **40% of patients with localized disease relapse**.
- **Local recurrences** occur in **less than 10%** of cases and the most frequent site of **metastasis** is the lung (**more than 80%** of cases).
- **Post-relapse survival (PRS)** after distant metastasis is poor. The **complete removal of all metastases**, **defined as a second complete surgical remission (CR-2)**, is the **main prognostic factor for PRS**.
- International guidelines stress the importance of an intensive follow-up program focusing on the chest and on the primary tumor site, particularly for the first 4–5 years.
- Currently, an **evidence-based follow-up policy is not available**. In clinical practice, **follow-up programs vary** in the different centers, both in terms of schedule and in terms of imaging techniques in use.

PATIENTS AND METHODS

Retrospective cohort analysis

Rizzoli Institute between 1986 and 2006 (20years)

INCLUSION CRITERIA

Patients who relapsed and between these, those who had lung metastases alone at time of the first recurrence.

Age up to 40 years

Localized high-grade osteosarcoma of the extremity

The imaging techniques used for chest surveillance changed over the study.

From 1986 to 1995 : Follow-up with chest X-ray.

- Every 2 months for the first 2 years, every 3 months the 3rd year, and then every 6 months. A confirmatory CT scan of the chest was performed in case of suspected nodules.

From 1996 to 2000 : Follow up with both chest X-ray and CT scan.

- CT of the chest, whereas those who were already followed by X-rays continued with the same technique.

Since 2001 to 2017 : Follow up only by CT.

- Every 3 months for the first 2 years, every 4 months in the 3rd and 4th year, then every 6 months.

Data collected:

- Date of the first surgical remission (CR-1)
- Date of the first recurrence
- Pattern of recurrence
- Imaging technique used for chest follow up (X-ray or CT)
- Relapse-free interval (RFI)
- Number and size of lung nodules
- Laterality
- Treatment at recurrence

- Relapse free interval (RFI) was calculated from the date of CR-1 to first relapse.
- Post relapse survival (PRS) was calculated from the date of first relapse to date of death or last follow-up.
- Overall survival (OS) was calculated from the date of CR-1 to date of death or last follow-up.
- Survival curves were compared by Kaplan and Meier.
- Chi square and *t* test were used for comparison between groups when appropriate.

The rate of patients who achieved CR-2, overall survival (OS), and post relapse survival (PRS) were the end-points of the study.

RESULTS

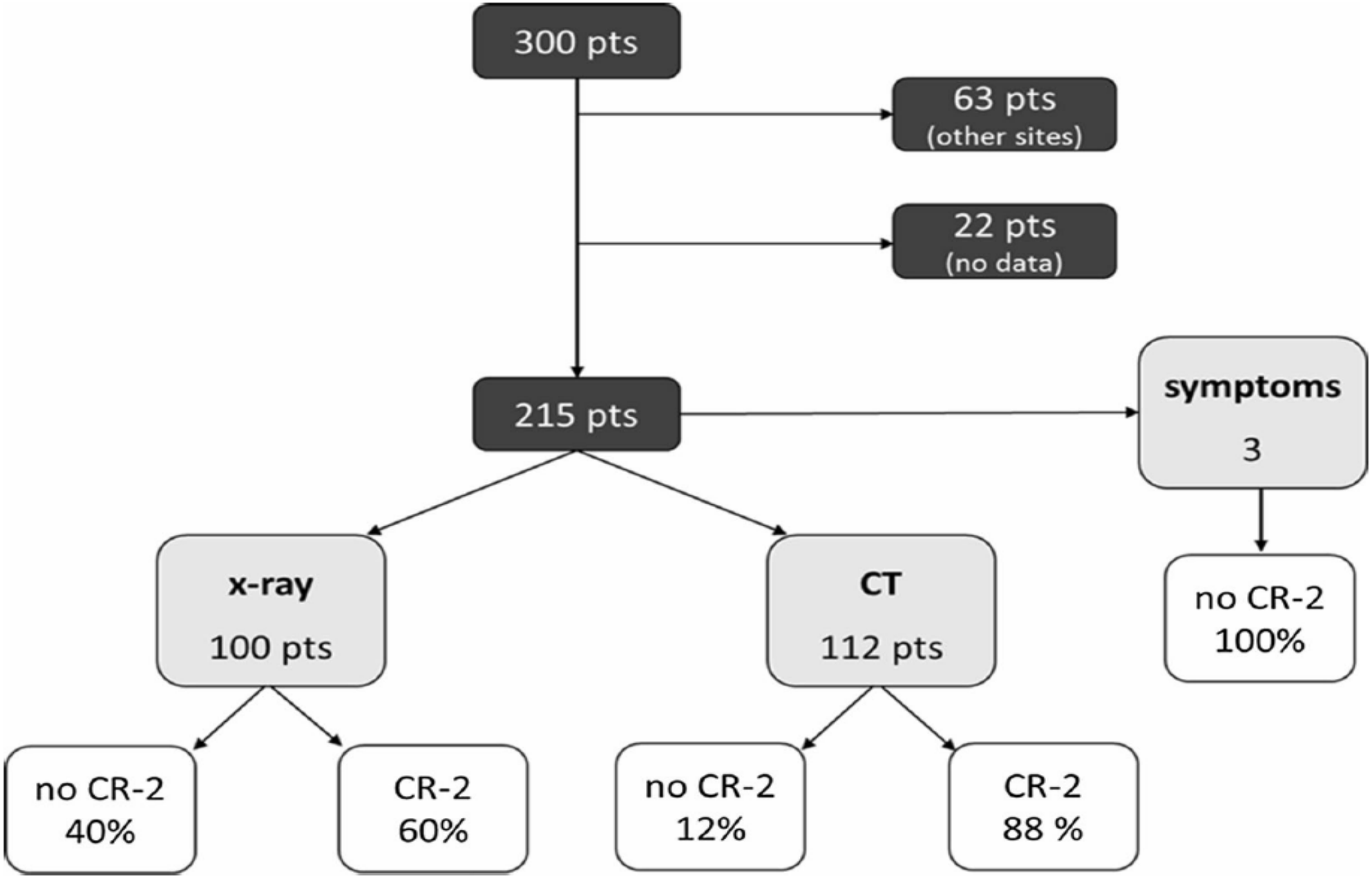

Fig. 1 Patients eligible for the analysis, method of lung metastases detection and rates of CR-2. *pts* patients, *X-ray* chest X-ray, *CT* chest computed tomography, *CR-2* second complete surgical remission

Table 1 Patient and disease features according to imaging technique used for follow-up

	X-ray 100 pts	CT 112 pts	p
Age (years)			
Range	6–43	6–42	.7
Median	15	16	
Sex			
F	42 (42%)	42 (38%)	.5
M	58 (58%)	70 (62%)	
Site			
Femur	49 (49%)	56 (50%)	.9
Tibia	30 (30%)	32 (29%)	
Humerus	16 (16%)	19 (17%)	
Other	5 (5%)	5 (4%)	
Histological response	(90 pts)	(94 pts)	.02
Good	62 (69%)	49 (52%)	
Poor	28 (31%)	45 (48%)	

pts patients, *X-ray* chest X-ray, *CT* computed tomography

Comparing the two groups of patients observed, no difference in terms of age, sex and site of the primary disease, while the rate of good responder patients was higher in the X-ray group compared to the CT group.

Table 2 Pattern of lung relapse according to imaging technique used for follow-up

	X-ray 100 pts	CT 112 pts	p
RFI			
Median (months)	28.4	22.3	.01
<2 years (pts)	49 (49%)	72 (64%)	.02
Laterality			
Monolateral	63 (63%)	88 (79%)	.01
Bilateral	37 (37%)	24 (21%)	
n. nodules (162 pts)	84 pts	78 pts	.4
1	52 (62%)	47 (60%)	
2–5	23 (27%)	21 (27%)	
>5	9 (11%)	10 (13%)	
Size (112 pts) (cm)	54 pts	58 pts	.03
<2	20 (37%)	37 (64%)	
2–5	26 (48%)	19 (33%)	
≥5	8 (15%)	2 (3%)	

pts patients, *X-ray* chest X-ray, *CT* computed tomography, *RFI* relapse free interval

At first recurrence, the number of lung nodules did not differ among the two groups, while the incidence of bilateral lung metastases was higher and nodules were larger when lung relapses were detected by chest X-ray. A shorter median RFI and a higher rate of patients with a RFI of <2 years observed in CT group. Relapse free interval of less than 2 years usually relate with a worse prognosis. The median RFI was shorter when patients were followed-up by CT, suggesting that the better prognosis observed in this group was probably due to the early diagnosis of recurrence, which led patients to be treated with surgery with radical intent more frequently with a higher rate of CR-2. Unilateral lesions of smaller size were more frequently detected in CT group, leading to a higher rate of surgical complete remission.

Table 3 Treatment and incidence of second complete surgical remission (CR-2) according to imaging technique used for follow-up

	X-ray 100 pts	CT 112 pts	p
Surgery			
Yes	73 (73%)	105 (94%)	<.0001
No	27 (27%)	7 (6%)	
1°line Chemo	(89 pts)	(104 pts)	.5
Yes	31 (35%)	41 (39%)	
No	58 (65%)	63 (61%)	
CR-2	60 (60%)	99 (88%)	<.0001

pts patients, *X-ray* chest X-ray, *CT* computed tomography, *Chemo* chemotherapy, *CR-2* second complete surgical remission

The percentage of patients who received chemotherapy at recurrence did not differ in the chest X-ray group compared with the CT group. Patients underwent surgery and achieved a CR-2 more frequently in the CT.

Table 4 Post relapse survival and overall survival at 3 and 5 years according to imaging technique used for follow-up

	X-ray 100 pts	CT 112 pts
PRS		
3-year PRS	33% (95% CI 33–42)	58% (95% CI 49–68)
5-year PRS	30% (95% CI 21–39)	49% (95% CI 39–59)
OS		
3-year OS	58% (95% CI 48–68)	72% (95% CI 63–80)
5-year OS	35% (95% CI 26–44)	60% (95% CI 51–70)

pts patients, *PRS* post relapse survival, *OS* overall survival, *CT* computed tomography, *95% CI* 95% confidence interval

The difference in terms of CR-2 translated in a significant difference in terms of PRS and OS between the two groups

DISCUSSION

- Results from the analysis show that routinely used chest CT scan, compared with X-ray, in the follow-up of osteosarcoma patients leads to a higher rate of second complete surgical remission (CR-2) and, consequently, to a significant benefit both in terms of PRS, and in terms of OS.
- One of the main aim of oncology follow-up is early detection of recurrence, especially when effective strategy of treatment can be offered. The study population was restricted on patients who had metastases confined to the lung to emphasize better the potential benefit related to early diagnosis with regard to the follow-up programs .It is well known that this group of patients has a better probability of survival compared to that reported for those with multiple metastatic sites.
- It is widely accepted that CT scan is superior to X-ray for the detection of lung nodules, but is under discussion whether the routine use of CT for chest surveillance can influence prognosis in patients with osteosarcoma. Data available in literature mainly comes from retrospective studies and only one prospective randomized study, which included both soft tissue and bone sarcomas.
- We are aware of the radiation risks related to the routine use of CT for chest surveillance, particularly in children and young adults. On the other hand, a 25% gain in terms of OS at 5 years as reported in our analysis indicated that the benefit related to the use of CT exceeded the risks of second malignancies associated.

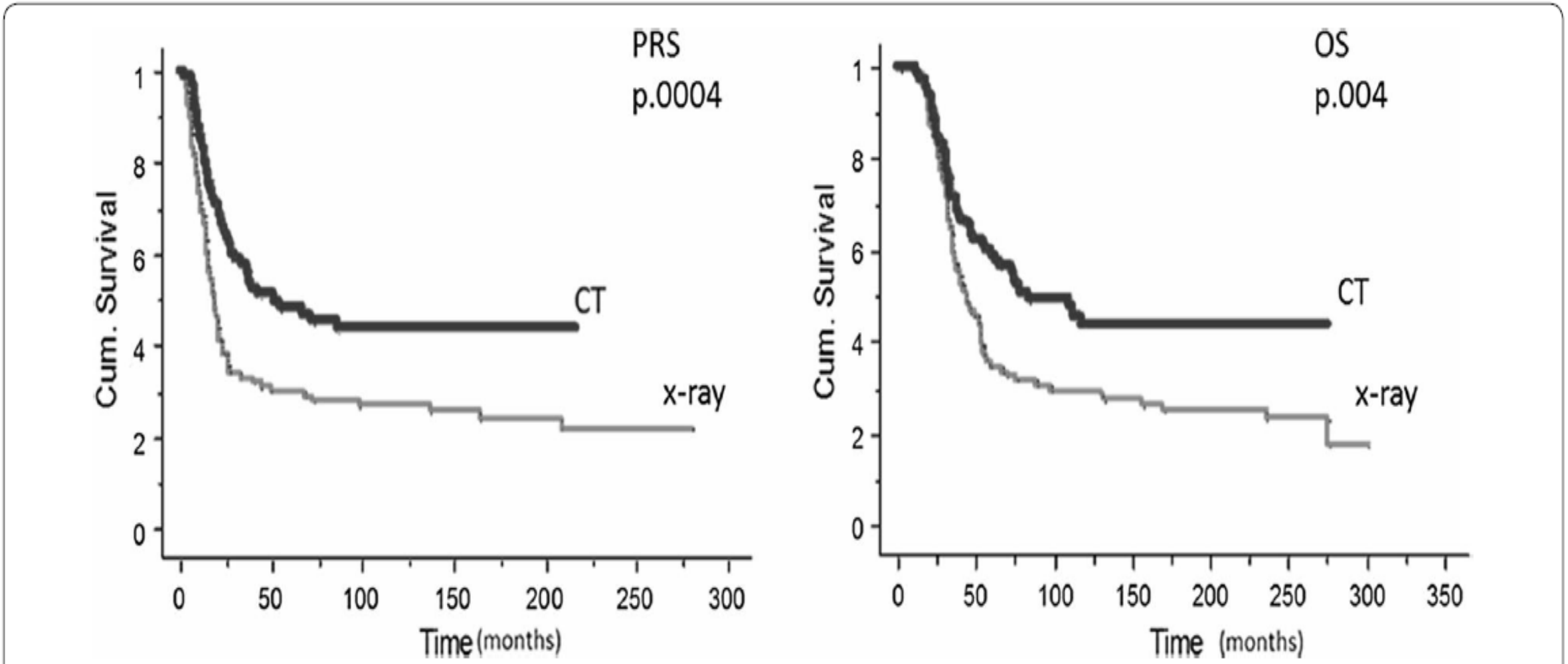

Fig. 2 Post relapse survival (PRS) and Overall survival (OS) at Kaplan and Meier analysis according to imaging technique used for follow-up. *PRS* post relapse survival, *OS* overall survival, *X-ray* chest X-ray, *CT* chest computed tomography

- A limit of our study is its retrospective design, and the long period of observation. A change in surgical techniques over the years could be a potential bias influencing results. However surgical procedures that allow the removal of metastases including a small amount of normal tissue around, like wedge resections, were available since early 1980s. The vast majority of the patients in our study, including patients who relapsed in the 1980s, were treated with wedge resections, monolateral or bilateral.

- It is important that the surgeon could evaluate the whole lung, in order to detect unrecognized nodules, for this reason no patient was treated with thoracoscopic resection.

- Surgery was the treatment of choice at the time of first recurrence, however some patients in our series were treated with chemotherapy. The rate of patient treated with first line chemotherapy did not differ among the two group of patients. On the other hands, it is questionable whether chemotherapy at the time of recurrence has an impact on post relapse survival. In a previous paper including patients evaluated in the present analysis, we could not observe any benefit from chemotherapy in patients surgically free of disease.
- A strength of our study is that we included a large and homogenous series of patients, treated and followed up in a single Institution. All patients had high grade localized osteosarcoma of extremity at diagnosis and lung metastases alone at first recurrence. The surgical directions did not changed over the study period. At the time of recurrence all the patients were evaluated in a multidisciplinary way together with the surgeon and, if indicated, they were treated by the same surgical team.
- In the group of patients followed-up with X-ray, in case of pathological findings, a confirmatory CT was performed. At the same way, in case of uncertain diagnosis when very small size nodules were detected in the CT group of patients, a new confirmatory CT was performed after 1 or 2 months, in order to evaluate the nodule growth.

CONCLUSION

In patients with high grade osteosarcoma of the extremity, a follow-up strategy based on chest CT allows a higher rate of second complete remission and significantly improves prognosis with a higher probability of post relapse and overall survival rate when compared to surveillance based on chest X-ray.

THANK YOU