

Plenary Session I (cont.)

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SURGERY ACCELERATES THE DEVELOPMENT OF PULMONARY METASTASES IN A MOUSE MODEL OF OSTEOSARCOMA AND IS ATTENUATED BY PERIOPERATIVE TREATMENT WITH GEFITINIB

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Purpose: Surgical resection of the primary tumor is often the first step in the treatment of solid cancers. However surgery itself may *promote* the growth of remote metastases, an effect referred to as surgery-accelerated metastasis. The development of pulmonary metastasis is the most common cause of mortality in patients with osteosarcoma (OS). We have demonstrated that macrophages promote OS invasion which can be blocked by modulating macrophage activity with the drug gefitinib. Furthermore, gefitinib reduced metastatic burden in a mouse model of OS. We examined the effect of surgery on the development of metastases and the impact of perioperative gefitinib in a mouse model of OS.

Methods: Mouse OS cells (K7M2) were implanted into the tibia of BALB/c mice (n=49). One week post-implantation mice were randomized to 5 groups (n=9-10/group): Group 1: control mice, no surgery; Group 2: Non-amputated mice treated with gefitinib; Group 3: resection of primary tumor via amputation; Group 4: Amputation of tumor-bearing limb plus gefitinib impregnated chow 2 days prior to amputation and continuing 7 days after surgery; Group 5: sham surgery with amputation of the contralateral limb. The lungs were harvested 3 weeks after amputation and the numbers of gross pulmonary metastases were counted.

Results: Mice that underwent amputation of the primary tumor had increased pulmonary metastases after 3 weeks when compared to control and sham-operated animals (20.8 vs 10.9 nodules; p<0.05, Fig 1). Perioperative administration of gefitinib decreased the effects of primary tumor removal on the development of pulmonary metastases (20.8 vs. 5.5 nodules; p<0.01, Fig 1). Surgical stress, represented by amputation of the contralateral limb, had no effect on metastasis.

Conclusions: Surgical removal of the primary tumor accelerates the growth of pulmonary metastases in a mouse model of osteosarcoma. Perioperative gefitinib treatment attenuates this effect. Neoadjuvant treatment with gefitinib may limit metastatic progression of osteosarcoma and improve survival.



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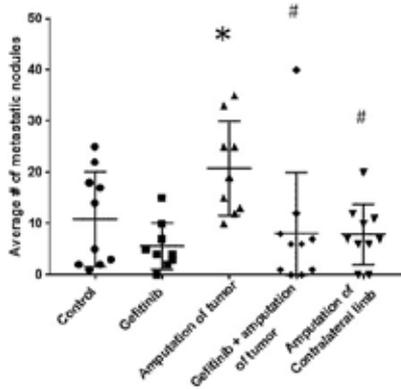


Figure 1. Amputation of the tumor-bearing limb increases the number of gross pulmonary metastases in a mouse model of OS, attenuated by perioperative gefitinib treatment. Data expressed as mean \pm SD (n=9-10/group); compared by one-way ANOVA. *p<0.05 vs. control; #p<0.05 vs. amputation of tumor.