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# The Design of a Phase I/II Trial of Neoadjuvant RT with Interdigitated Multiple Fractions of Lattice RT for Large High-grade Soft-Tissue Sarcoma

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**Abstract :** Soft Tissue Sarcomas (STS) represent a diverse group of malignancies with heterogeneous clinical and pathological features. The treatment of extremity STS aims to achieve optimal local tumor control, improved survival, and preservation of limb function. The National Comprehensive Cancer Network guidelines, based on the cumulated clinical data, recommend radiation therapy (RT) in conjunction with limb-sparing surgery for large, high-grade STS measuring greater than 5 cm in size. Such treatment strategy can offer a cure for patients. However, when recurrence occurs (in nearly half of patients), the prognosis is poor, with a median survival of 12 to 15 months and with only palliative treatment options available. The spatially-fractionated-radiotherapy (SFRT), with a long history of treating bulky tumors as a non-mainstream technique, has gained new attention in recent years due to its unconventional therapeutic effects, such as bystander/abscopal effects. Combining single fraction of GRID, the original form of SFRT, with conventional RT was shown to have marginally increased the rate of pathological necrosis, which has been recognized to have a positive correlation to overall survival. In an effort to consistently increase the pathological necrosis rate over 90%, multiple fractions of Lattice RT (LRT), a newer form of 3D SFRT, interdigitated with the standard RT as neoadjuvant therapy was conducted in a preliminary clinical setting. With favorable results of over 95% of necrosis rate in a small cohort of patients, a Phase I/II clinical study was proposed to exam the safety and feasibility of this new strategy. Herein the design of the clinical study is presented. In this single-arm, two-stage phase I/II clinical trial, the primary objectives are >80% of the patients achieving >90% tumor necrosis and to evaluation the toxicity; the secondary objectives are to evaluate the local control, disease free survival and overall survival (OS), as well as the correlation between clinical response and the relevant biomarkers. The study plans to accrue patients over a span of two years. All patient will be treated with the new neoadjuvant RT regimen, in which one of every five fractions of conventional RT is replaced by a LRT fraction with vertices receiving dose ≥10Gy while keeping the tumor periphery at or close to 2 Gy per fraction. Surgical removal of the tumor is planned to occur 6 to 8 weeks following the completion of radiation therapy. The study will employ a Pocock-style early stopping boundary to ensure patient safety. The patients will be followed and monitored for a period of five years. Despite much effort, the rarity of the disease has resulted in limited novel therapeutic breakthroughs. Although a higher rate of treatment-induced tumor necrosis has been associated with improved OS, with the current techniques, only 20% of patients with large, high-grade tumors achieve a tumor necrosis rate exceeding 50%. If this new neoadjuvant strategy is proven effective, an appreciable improvement in clinical outcome without added toxicity can be anticipated. Due to the rarity of the disease, it is hoped that such study could be orchestrated in a multi-institutional setting.

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