The goal in radiotherapy for cancer is to maximize tumor-kill while limiting toxic effects on nearby healthy anatomies. This is attempted via a two-pronged approach: spatial localization of radiation dose, and temporal dispersion of radiation dose. The spatial component involves prescribing a high dose to the tumor and putting upper limits on the dose delivered to the healthy anatomies. The radiation field’s intensity profile is then optimized to meet this treatment protocol as closely as possible. This is called fluence-map optimization. The temporal component of the problem involves breaking the total planned dose into several equal-dose treatment sessions called fractions that are administered over several weeks. This gives the healthy tissue some time to recover between sessions, as it possesses better damage-repair capabilities than the tumor. The key challenge on this temporal side is to choose an optimal number of fractions and the corresponding dosing schedule. This is called the optimal fractionation problem. In this talk, I will discuss several spatiotemporally separated and integrated mathematical formulations and corresponding solution methods for this problem. This talk is based on joint work with several former graduate students. (Received January 28, 2019)