Talking Points for Physicians Enrolling Patients to ACOSOG Z4099/RTOG 1021

Patient with early stage lung cancer can be divided into 3 groups based on their surgical risks:

1. *Average risk*: can likely tolerate a lobectomy
2. *High risk operable*: would be at high-risk for lobectomy, but could potentially tolerate a sublobar resection (anatomical segmentectomy or non-anatomical wedge resection)
3. *Medically Inoperable*: cannot tolerate any potentially curative resection due to co-existing medical problems

ACOSOG Z4099/RTOG 1021 is specifically for high risk operable patients and randomly assigns patients to either sublobar resection or stereotactic ablative radiotherapy (SABR, aka, stereotactic body radiation therapy, SBRT).

While opinion among surgeons varies about the criteria for assigning patients into a particular risk category, all patients enrolled to this trial must meet the protocol eligibility.

The protocol study team does not wish to create controversy in the protocol defined assignments of risk which could jeopardize the likelihood of a patient accepting the randomized treatment assignment. As such, in the opinion of the treating surgeon, patients enrolled to this trial should not be *average risk* (more appropriately treated with lobectomy) or *medically inoperable* (more appropriately treated with non-surgical therapies).

The trial will analyze patients in two categories based on intent to treat, not actual treatment delivered. As such, it is important to fully inform patients prior to enrollment so that they accept the randomized assignment and follow-up requirements.

The SABR treatment used in ACOSOG Z4099/RTOG 1021 is based on the same treatment delivered to medically inoperable patients with stage I non-small cell lung cancer in RTOG 0236.

The SABR treatment is delivered in 3 outpatient treatments given 2-4 days apart (e.g., Monday, Thursday, Monday). Each treatment takes about an hour.

Facts about SABR

SABR was developed in the mid 1990s using image and motion guidance in addition to radiation delivery techniques employed for highly accurate and precise stereotactic radiosurgery for brain tumors. SABR employs:

1. secure immobilization avoiding patient movement for the typical long treatment sessions
2. accurate repositioning from simulation to treatment
3. minimization of normal tissue exposure attained by using multiple (eg, 10 or more) or large-angle arcing small aperture fields
4. rigorous accounting of organ motion
5. stereotactic registration (ie, via fiducial markers or surrogates) of tumor targets and normal tissue avoidance structures to the treatment delivery machine
6. ablative dose fractionation delivered to the patient with subcentimeter accuracy.

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SABR is currently in widespread, worldwide use to treat primary and metastatic tumors in the lung, liver, and spine.

SABR requires special equipment, techniques, and training to be performed safely and effectively. These special features are necessary because SABR has radiobiological characteristics very distinct from historically available conventionally fractionated radiation therapy.

Unlike conventional radiotherapy which treats the tumor along with relatively large volumes of normal tissue to the same dose trying to exploit differences in tumor and normal tissue response, SABR is ablative (destructive) making it necessary to aggressively limit the volume of normal tissue (lung) included in the high dose.

Even though SABR is extremely potent radiation delivery, it appears to be safer than conventionally fractionated radiation in medically inoperable patients because of the measures to reduce normal lung volume irradiated.

Prospective trials have been carried out in several countries worldwide showing SABR can control primary lung cancer within the radiation field in 80-90% of patients treated with adequate ablative dose.

Tumor "control" with SABR is defined as failure to progress with long term follow-up.

In most cases treated with SABR, initial scans (e.g., 3 months after therapy) show dramatic tumor shrinkage. However, with longer follow-up radiographic changes consistent with atelectasis and fibrosis occur in the vicinity of the treated tumor possibly making the actual tumor less visible.

Survival in medically inoperable patients with early stage lung cancer was 56% at 3 years in the RTOG 0236 study. This is nearly double historically reported survival rates for conventionally fractionated radiotherapy. Since the treated patients were exclusively medically inoperable, they had competing causes of death unrelated to their lung cancer.

It is anticipated that survival with SABR in the more favorable high risk operable population studied in Z4099-1021 will be higher than in RTOG 0236.

Patients in most SABR series are clinically staged (typically with CT/.PET) rather than pathologically staged as in surgical series. Patients in Z4099-1021 may be clinically or pathologically staged per the enrolling physician's discretion. However any suspicious lymph nodes seen on CT and /or PET scan will need pathological confirmation that these nodes have no evidence of disease

Despite clinical staging, only 2 out of 56 patients on RTOG 0236 experienced failure in the hilum or mediastinum. As with most surgical series, the primary mode of failure was disseminated. Patterns of failure after SABR treatment in 56 patients in RTOG 0236 is shown in the figure.

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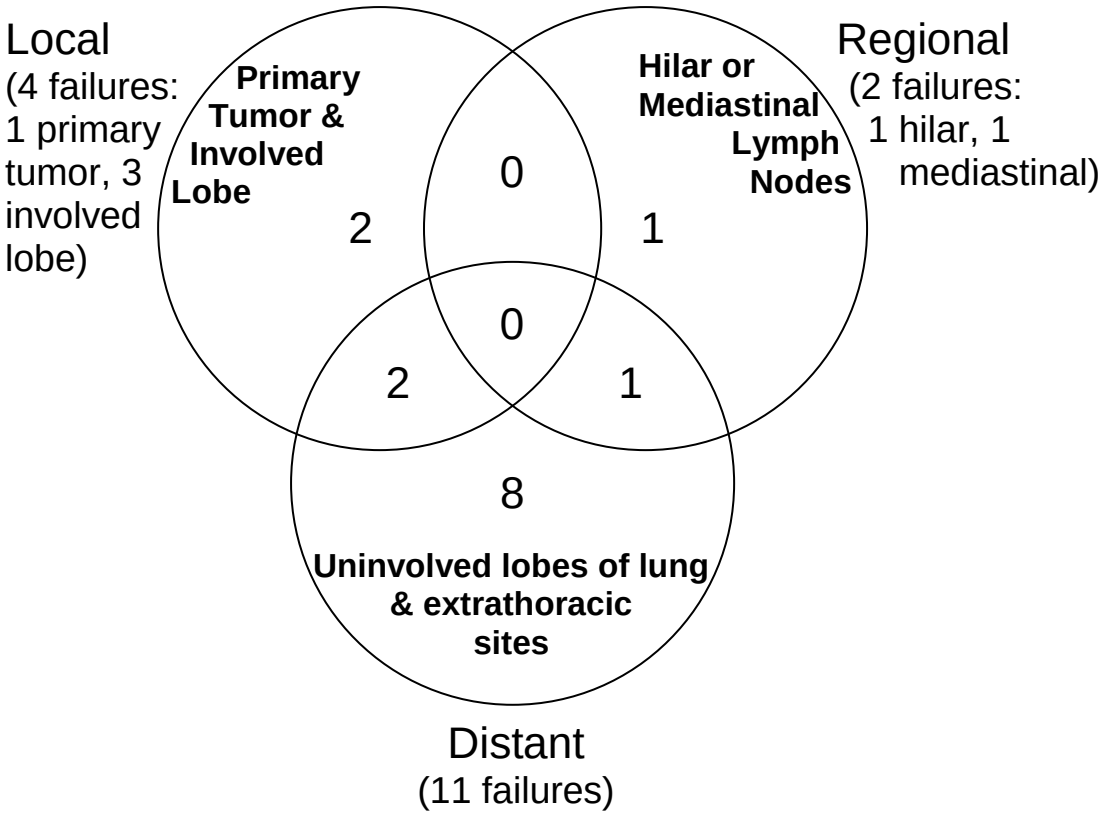

Most side effects related to SABR do not occur for 6-9 months post treatment. In RTOG 0236, the most common serious side effects were decline in pulmonary function tests (typically DLCO and not spirometry), pneumonia, radiation pneumonitis, and chest wall pain (possibly related to rib fracture). Serious side effects requiring hospitalization occurred in about 15% of treated medically inoperable patients.

SABR has been used in two completed, prospective trials in operable patients conducted by cooperative oncology groups. The RTOG 0618 trial was a small pilot trial that completed enrollment in 2010 but has not been reported. The JCOG 0403 trial from Japan enrolled exclusively stage Ia patients and was presented at the 2010 ASTRO meeting but has not been published. It showed overall survival of 76% at 3 years but only 83% local control. However, the dose used in this trial was considerably less potent than for Z4099-1021. Using the 54 Gy in 3 fractions dose, local control (i.e., failure in the primary site and anywhere else in the involved lobe) in RTOG 0236 was 91% at 3 years.

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