Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials


Summary

Background The standard of care for operable, stage I, non-small-cell lung cancer (NSCLC) is lobectomy with mediastinal lymph node dissection or sampling. Stereotactic ablative radiotherapy (SABR) for inoperable stage I NSCLC has shown promising results, but two independent, randomised, phase 3 trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) closed early due to slow accrual. We aimed to assess overall survival for SABR versus surgery by pooling data from these trials.

Methods Eligible patients in the STARS and ROSEL studies were those with clinical T1–2a (<4 cm), N0M0, operable NSCLC. Patients were randomly assigned in a 1:1 ratio to SABR or lobectomy with mediastinal lymph node dissection or sampling. We did a pooled analysis in the intention-to-treat population using overall survival as the primary endpoint. Both trials are registered with ClinicalTrials.gov (STARS: NCT00840749; ROSEL: NCT00687986).

Findings 58 patients were enrolled and randomly assigned (31 to SABR and 27 to surgery). Median follow-up was 40·2 months (IQR 23·0–47·3) for the SABR group and 35·4 months (18·9–40·7) for the surgery group. Six patients in the surgery group died compared with one patient in the SABR group. Estimated overall survival at 3 years was 95% (95% CI 85–100) in the SABR group compared with 79% (64–97) in the surgery group (hazard ratio [HR] 0·14 [95% CI 0·017–1·190], log-rank p=0·037). Recurrence-free survival at 3 years was 86% (95% CI 74–100) in the SABR group and 80% (65–97) in the surgery group (HR 0·69 [95% CI 0·21–2·29], log-rank p=0·54). In the surgery group, one patient had regional nodal recurrence and two had distant metastases; in the SABR group, one patient had local recurrence, four had regional nodal recurrence, and one had distant metastases. Three (10%) patients in the SABR group had grade 3 treatment-related adverse events (three [10%] chest wall pain, two [6%] dyspnoea or cough, and one [3%] fatigue and rib fracture). No patients given SABR had grade 4 events or treatment-related death. In the surgery group, one (4%) patient died of surgical complications and 12 (44%) patients had grade 3–4 treatment-related adverse events. Grade 3 events occurring in more than one patient in the surgery group were dyspnoea (four [15%] patients), chest pain (four [15%] patients), and lung infections (two [7%]).

Interpretation SABR could be an option for treating operable stage I NSCLC. Because of the small patient sample size and short follow-up, additional randomised studies comparing SABR with surgery in operable patients are warranted.

Funding Accuray Inc, Netherlands Organisation for Health Research and Development, NCI Cancer Center Support, NCI Clinical and Translational Science Award.

Introduction

Standard therapy for operable, clinical stage I, non-small-cell lung cancer (NSCLC) is lobectomy with sampling or dissection of mediastinal lymph nodes. During the past decade, stereotactic ablative radiotherapy (SABR; also called stereotactic body radiotherapy) has resulted in local control in excess of 90% of tumours with medically inoperable and operable clinical stage I NSCLC.1–4 Overall survival after SABR is better than after conventional radiation.5 SABR delivers ablative doses of radiation (biologically effective dose [BED] >100 Gy) to tumours in one to ten fractions. Several radiation fields (or arcs) are delivered from various angles to converge on a target, and the dose distribution is further adjusted so that the dose is sharply reduced within a few mm beyond the target, sparing nearby, crucial, normal structures from radiation-induced damage. Findings from retrospective and phase 2 prospective studies have shown that SABR is associated with overall survival similar to that of surgery in patients with operable stage I NSCLC.1–4,6–9 Findings from population-based studies and propensity-matched analyses suggest that overall survival and disease-specific survival after SABR are similar to those after surgery.5,6,10 However, concerns remain about the risk of local or nodal recurrence after SABR, either of which could lead to worse overall survival than after standard surgery. So far, three phase 3 randomised studies have been initiated to compare SABR with surgery in patients with early-stage NSCLC (the STARS trial [NCT00840749], the ROSEL trial [NCT00687986],...
and the ACOSOG Z4099 trial [NCT01336894]), but all were closed early because of slow accrual. Because the entry criteria for the STARS and ROSEL trials were similar, we aimed to combine and analyse data from these two trials to assess overall survival, patterns of failure, and toxic effects.

Methods
Study design and and participants
Both trials (STARS and ROSEL) included in this pooled analysis were open-label, randomised, phase 3 trials of SABR versus surgery for patients with early-stage NSCLC. Histological confirmation of NSCLC by biopsy or cytological evaluation was required in the STARS trial but was not mandatory in the ROSEL protocol. In the ROSEL trial, which included only Dutch patients, patients for whom no pathological confirmation of diagnosis was available were eligible if they had a new or growing pulmonary lesion with radiological features consistent with malignant disease and avidity on ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG-PET), because the likelihood of a benign diagnosis in such cases in the Dutch population is less than 6%. All NSCLC histological subtypes were eligible. All patients had to have appropriate staging studies including chest CT and ¹⁸F-FDG-PET, identifying them as having T1–2a (<4 cm), N0M0, operable disease according to the 7th edition of the American Joint Committee on Cancer–International Association for the Study of Lung Cancer staging classifications. Patients with radiologically suspicious lymph nodes underwent endobronchial ultrasonography or mediastinoscopy. Detailed eligibility and exclusion criteria are included in the appendix.

Added value of this study
Both single-arm, phase 2 studies, and retrospective analyses, have shown efficacy and safety of SABR in operable stage I NSCLC. Findings from several non-randomised studies have suggested similar overall survival after either SABR or surgery, but were confounded because of potential patient selection bias. Three phase 3 randomised studies comparing the two treatments have failed to complete accrual. Despite its limitations, to our knowledge this analysis is the first and only randomised evidence comparing SABR with surgery in operable patients who are fit for surgery.

Implications of all the available evidence
The results of this combined analysis of STARS and ROSEL suggest that SABR can be considered a treatment option in operable patients needing a lobectomy. The equipoise suggested by our results justifies efforts for additional randomised clinical trials.

For the STARS trial, 28 sites in the USA, China, and France were approved for patient enrolment, and seven enrolled patients; for the ROSEL trial, ten centres in the Netherlands were approved, and four enrolled patients (appendix). All patients provided written informed consent. The institutional review board of MD Anderson Cancer Center and the Medical Ethics Committee at the VU University Medical Center provided ethical oversight for conduct of the STARS and ROSEL studies, respectively. No specific oversight was provided for the statistical analysis, but all STARS and ROSEL coauthors were provided with the study report, and were involved in updating individual data of included patients.
randomised by the trial office at the Netherlands Cancer Institute. Patients were subsequently randomly assigned in a 1:1 ratio with the TENALEA randomisation system to receive SABR or surgery. Randomisation was done with the minimisation method, stratified by institute, histological type (squamous cell, non-squamous cell, or other), and WHO performance status (0, 1, or 2). No allocation sequence was generated in advance. Each participant was randomised separately at the time of enrolment.

Procedures

For patients randomly assigned to receive surgery, acceptable surgical techniques included anatomic lobectomy by open thoracotomy or video-assisted thoracotomy. All accessible hilar (level 10) lymph nodes had to be dissected from the specimen. All patients who had a lobectomy also underwent dissection or sampling of mediastinal lymph nodes in both trials (for right-sided lesions, including levels 4R, 7, and 9; for left-sided lesions, including 5, 6, 7, and 9).

In the STARS protocol, the CyberKnife system (Accuray, Sunnyvale, CA, USA) was used for all radiotherapy sessions for patients randomly assigned to receive SABR. Implant fiducial markers were used to verify and track tumour motion. Patients with peripherally located lesions (ie, those located >2 cm in any direction from the proximal bronchial tree, major vessels, oesophagus, heart, tracheal, vertebral body, pericardium, mediastinal pleural, and brachial plexus) received a total radiation dose of 54 Gy in three 18 Gy fractions (BED 151·2 Gy), calculated with a Monte Carlo or equivalent algorithms or its equivalent dose if other algorithms were used and heterogeneity correction. For central lesions (ie, those within 2 cm of these structures), 50 Gy in four 12·5 Gy fractions (BED 112·5 Gy) was used. The SABR dose was prescribed to the highest isodose line, which was required to cover 100% of the gross tumour volume (defined as visible disease in CT images with use of lung window) and more than 95% of the planning target volume (defined as the gross tumour volume plus a 3 mm margin). Coverage of 100% of the planning target volume by at least the prescription dose was encouraged. The normal tissue constraints were met for all cases. Treatment delivery was recommended to be complete within 5 days of its initiation.

In the ROSEL protocol, linear-accelerator-based SABR from multiple vendors was used for patients randomly assigned to receive surgery.
assigned to receive radiotherapy. Only lesions located 2 cm or more from the hilar structures on the diagnostic CT scan were eligible. A toxicity risk-adapted fractional scheme was used in which a total dose of 54 Gy in three 18 Gy fractions (BED 151·3 Gy), calculated with a Monte Carlo or equivalent algorithms or its equivalent doses if other algorithms were used and heterogeneity correction, and given over 5–8 days; alternatively, a total dose of 60 Gy at five 12 Gy fractions (BED 132·0 Gy), was given over 10–14 days (to account for different treatment-delivery practices in Dutch centres). The SABR dose prescription was chosen such that 95% of the planning target volume, the internal target volume (based on four-dimensional CT), or other equivalent approaches to take tumour motion into consideration—plus a 3–5 mm margin for setup and motion uncertainty—would receive at least the nominal fraction dose, and 99% of the planning target volume would receive at least 90% of the fraction dose. The preferred maximum dose within the planning target volume was between 110% and 140% of the prescribed dose. Additional details about the radiotherapy procedures are provided in the appendix.

In the STARS trial, patients were followed up every 6 months for 2 years, and then annually thereafter. Contrast-enhanced CT of the chest and upper abdomen or PET-CT images were obtained at the 6-month and subsequent follow-up visits.8 The first patient was enrolled on Sept 10, 2009. Enrolment was closed in Jan 16, 2013, and the last follow-up was done on July 14, 2014.

In the ROSEL trial, clinical follow-up visits took place every 3 months for the first year after treatment and then every 6 months for the following 60 months. Each follow-up visit included contrast-enhanced CT scans of the thorax and upper abdomen. The first patient was enrolled on Oct 7, 2008. Enrolment was closed on Dec 10, 2010, and last follow-up was done on April 16, 2014. Adverse events in both protocols were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (CTCAE v3).

### Outcomes

The primary outcome measure for this pooled analysis was overall survival according to treatment group (SABR vs surgery). Secondary outcome measures included recurrence-free survival, and grade 3 or worse acute or chronic toxicity.

### Statistical analysis

We based our analysis of primary outcomes, secondary outcomes, and safety on the intention-to-treat population, comprising all patients who were enrolled and randomly assigned. We used all individual patient data available from the two randomised controlled trials. The analyses were exploratory in nature, without power, sample size, or sensitivity calculation.

We calculated overall survival from the date of treatment to last contact date (death date or last follow-up date, at which point patients who were still alive were censored). We calculated time to local recurrence within the same lobe, time to regional recurrence, and time to distant metastasis from date of treatment to date of first recurrence or last assessment date. Patients who did not have recurrence or metastases were censored at the date of death or last follow-up. We calculated recurrence-free survival from date of treatment to date of first recurrence or last contact date. For patients who did not have a recurrence but died, we calculated recurrence-free survival from the date of treatment to the date of death. Patients who did not have a recurrence or distant metastases and did not die were censored at the last follow-up date.

Summary statistics were provided with frequency count and percentage for categorical variables, and mean, SD, median, and range for continuous variables. We used Fisher’s exact test or the χ² test to assess
associations between two categorical variables. We used the Wilcoxon rank sum test to evaluate the difference in a continuous variable between two patient groups. We used the Kaplan-Meier method to estimate overall survival and recurrence-free survival, and time to local recurrence, regional recurrence, and distant metastasis, and used log-rank tests to evaluate differences in time-to-event outcomes between surgery and SABR with two-sided p values. We classified p values less than 0·05 as statistically significant. We also calculated hazard ratios (HRs) with 95% CIs with a Cox proportional hazards model. We used statistical software SAS 9.1.3 and S-Plus 8.0 for the analyses. Complete statistical methods are given in the appendix.

Both trials are registered with ClinicalTrials.gov (STARS: NCT00840749; ROSEL: NCT00687986).

Role of the funding source

This analysis was designed by the principal and coprincipal investigators of both trials. The design and analysis of the STARS protocol involved biostatisticians funded by Accuray and Varian Medical Systems. Follow-up analyses of the STARS protocol were funded by a grant from Varian Medical Systems. The STARS trial was funded by Accuray and the ROSEL study by the Netherlands Organisation for Health Research and Development. For the STARS protocol, Accuray specified that the CyberKnife platform was the sole platform to be used for the study, but did not have a role in any other aspect of the study design. The funding body of ROSEL solicited responses from national and international external reviewers, but did not otherwise have any role in the design of the trial. Beyond providing financial support, neither funder was involved in accessing the raw data, collection, analysis, or interpretation of the data, or writing of the report. The corresponding author had full access to all of the data and the final responsibility for the decision to submit for publication.

Results

58 patients were enrolled and randomly assigned in the combined studies (31 to SABR and 27 to surgery; figure 1). We did not note any differences in age, sex, performance status, histology, T stage, or tumour location between the two treatment groups (table) or between the two trials (appendix). Median follow-up for all patients was 40·2 months (IQR 23·0–47·3) in the SABR group and 35·4 months (18·9–40·7) in the surgery group. All patients had stage I NSCLC (\(<4 \text{ cm}\) ), and were thought medically operable for lobectomy with performance status of 0 to 2. 18F-FDG-PET was used for the staging but information about maximal standardised uptake value was not collected because of substantial variation in the PET procedures. Of the 27 patients who received surgery, 19 had open lobectomies, five had video-assisted thoracotomy lobectomies, one had video-assisted thoracotomy biopsy (mediastinal lymph node biopsy positive for metastatic lung cancer), one had open wedge resection (benign lung nodule), and one had an aborted resection during the surgery due to disease progression. In the STARS trial, 16 patients had peripherally located lesions and so received 54 Gy in three fractions, and four had central lesions and so received 50 Gy in four fractions. In the ROSEL trial, six patients received 54 Gy in three 18 Gy fractions over 5–8 days, and five patients received 60 Gy at five 12 Gy fractions over 10–14 days due to variation in centre protocol.

Pooled estimated overall survival at 1 year and 3 years was 100% (95% CI 100–100) and 95% (95% CI 85–100) in the SABR group, and 88% (95% CI 77–100) and 79% (95% CI 64–97) in the surgical group (figure 2). The difference in overall survival between the two groups was statistically significant (log-rank p=0.037; HR 0·14 [95% CI 0·017–1·190]). The difference in overall survival between two groups was significant in STARS alone (log-rank p=0.0067) but not in ROSEL alone (log-rank p=0.78; appendix). Seven patients died during study follow-up: six in the surgery group (two from cancer progression, one from secondary primary lung cancer, one from a surgical adverse event, and two from comorbidities) and one in the SABR group (from cancer progression). Median overall survival was not reached for either treatment group.

Figure 2: Overall survival (A) and recurrence-free survival (B)
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR=stereotactic ablative radiotherapy. HR=hazard ratio.
In the SABR group, one patient had local recurrence, four had regional nodal recurrence and one had distant metastases. In the surgery group, one patient had regional nodal recurrence and two had distant metastases. In the surgery group, one patient (96% [95% CI 89–100] free from distant metastasis at 3 years) compared with 80% (95% CI 65–97) in the surgery group (HR 0.69 [95% CI 0.21–2.29]; six events; log-rank p=0.54). Because of the small number of events, the statistical power to detect significant differences in frequency of local, regional, and distant failure between the two groups was low. The relapse frequencies and recurrence-free survival are preliminary because of short follow-up.

A single local recurrence in the SABR group was salvaged by lobectomy. Three patients with recurrence in isolated regional lymph nodes in the SABR group were treated with concurrent chemoradiotherapy, and two remained free of disease. Two patients (one each from the SABR and surgery groups) developed both regional and distant metastases, and were treated with chemotherapy and palliative radiotherapy. Two patients from the surgery group had secondary primary lung cancers and were treated with SABR (one patient) and concurrent chemoradiotherapy (one patient). One patient from the SABR group developed secondary primary lung cancer and was re-treated with SABR.

In the SABR group, three (10%) patients had treatment-related grade 3 adverse events: two (6%) patients developed grade 3 dyspnoea or cough, three (10%) had grade 3 chest wall pain, and one (3%) had grade 3 fatigue and a rib fracture. No patients in the SABR group experienced treatment-related grade 4 toxic effects or treatment-related death. In the surgery group, one (4%) patient died of surgical complications and 12 (44%) patients had grade 3–4 treatment-related adverse events. One (4%) patient in the surgery group developed grade 4 dyspnoea, four (15%) developed grade 3 dyspnoea, two (7%) developed grade 3 lung infections, and four (15%) had grade 3 chest pain. Other treatment-related grade 3 toxic effects in the surgery group included bleeding, fistula, hernia, anaemia, fatigue, nausea, weight loss, and cardiac arrhythmias (one case each).

We did not find any significant differences in frequency of local, regional, or distant metastasis or in recurrence-free survival between the treatment groups (figures 2, 3). At 3 years, 96% (95% CI 89–100) of patients in the SABR group were free from local recurrence (only one patient had local recurrence) compared with 100% (95% CI 100–100) of patients in the surgery group (log-rank p=0.44). Four patients in the SABR group developed regional nodal recurrence (90% [95% CI 80–100] free from regional recurrence at 3 years) compared with one patient in the surgery group (96% [95% CI 89–90]) at 3 years; HR 2.89 [95% CI 0.32–26.01]; log-rank p=0.32).

Discussion

To our knowledge, this report is the first analysis of data from phase 3 randomised trials comparing SABR with surgery, and also the first report to suggest that SABR is better tolerated and might lead to better overall survival compared with surgery for operable clinical stage I NSCLC. The results of this analysis are compatible with the notion that the two therapies are equally effective, with lower survival after surgery possibly resulting from comorbidities worsened by the surgical reduction of lung function. However, because of the small patient sample size and short follow-up, these conclusions should be interpreted cautiously. Our findings nevertheless
strongly suggest at least equipoise between the two modalities and support the initiation of larger randomised studies to validate these findings. Although stratification criteria, pathology requirements, and the follow-up schedule were not identical between STARS and ROSEL, they were similar. Because stratification was done by each centre before randomisation to SABR or surgery, these minor differences should not substantially affect the clinical outcomes.

On the basis of our findings and the published scientific literature, lobectomy with mediastinal node dissection or sampling—the standard of care for patients with operable clinical stage I NSCLC—results in an increased rate of procedure-related mortality and morbidity compared with SABR. Findings from a systematic review of video-assisted thoracotomy and open thoracotomy lobectomy suggested complications in 16·4% and 31·2% of patients, respectively, and a national database showed corresponding complication incidences of 40·8% and 45·1%. Morbidity associated with surgery includes atrial fibrillation, postoperative pneumonia, myocardial infarction, deep venous thrombosis, and pulmonary embolism. Even with minimally invasive surgical techniques, operative mortality rates within 30 to 90 days after surgery are 2% to 5·4%. SABR, however, had a 0·7% cumulative procedure-related mortality in a meta-analysis and has the added benefit of lung preservation in a patient population that frequently has compromised pulmonary function. When SABR is delivered with the planning target volume receiving BED more than 100 Gy and the tolerance of normal tissue respected, it results in local control in more than 90% of tumours with very little acute or chronic severe toxicity. SABR has emerged as a non-invasive standard treatment alternative to surgery for elderly patients and for patients with clinically significant comorbidities.

After surgery, patients with stage I NSCLC are at risk for recurrence, with rates ranging from 6% to 10% per person-year during the first 4 years, with 5% to 10% of patients eventually developing local-regional recurrence, and 10% to 20% distant metastasis in the first 4 years. Although recurrence within the planning target volume after SABR is uncommon, concerns have been raised about recurrences in the same lobe, in the hilum, and in the mediastinum, because these areas are not treated. Moreover, surgical patients typically undergo additional staging during surgery via mediastinal nodal sampling or dissection, whereas patients receiving SABR typically undergo clinical staging with CT, PET-CT, and endobronchial ultrasonography. Because false-negatives and false-positives associated with ¹⁸F-FDG-PET scanning (estimated at 10–30% for both) could lead to stage migration, surgical staging could lead to upstaging of disease that might be useful to guide the choice of adjuvant therapy. Endobronchial ultrasonography could reduce the frequency of false-negatives or false-positives for PET-CT in clinical lymph node staging. However, even with local or regional lymph node recurrence after SABR, salvage lobectomy or definitive radiotherapy to the primary site, regional lymph nodes, or both can be done and survival might not be compromised.

Analyses of single-group trials suggest that outcomes after SABR can equal those of surgery. Findings from a review of medically operable patients who received SABR in a multi-institutional study in Japan showed 5-year local recurrence and overall survival of 8·4% and 70·8%, respectively. These outcomes are similar to the 5-year outcomes observed for the lobectomy group of the North American Lung Cancer Study Group 821 trial (6% local recurrence and 70% overall survival). Findings from prospective phase 2 studies in operable stage I NSCLC treated by SABR, including the Japanese Clinical Oncology Group 0403 trial and Radiation Therapy Oncology Group trial 0618, have shown overall survival to be between 76% and 85% at 3 years, also similar to surgery. The 3 year overall survival noted in our study is better than that from previous trials, a finding that could be due to smaller lesions included in the current study, better performance status, more accurate pretreatment staging, and lower comorbidities in the so-called standard-risk surgical patients. Studies using propensity-score matching methodology with large patient populations from different continents have shown similar rates of overall survival between SABR and lobectomy with either open surgery or video-assisted thoracotomy.

A definitive answer to the question of whether outcomes from SABR are equivalent to surgery for stage I NSCLC will require a larger randomised study. Unfortunately, all randomised studies comparing SABR with surgery to date have closed prematurely because of slow enrolment. Undoubtedly the substantial procedure differences (outpatient treatment vs thoracic surgery) between these two treatment modalities have made it difficult for physicians and patients to be free of bias when considering enrolment. Although this study is limited by the small number of enrolled patients and requires validation with larger numbers of patients, our findings strongly support equipoise between surgery and SABR and justify the initiation of large randomised comparisons of surgery versus SABR. Two new randomised studies are currently in preparation and are expected to be opened in 2015: VALOR (Veterans Affairs Lung cancer surgery Or stereotactic Radiotherapy trial; Mghanaki D, personal communication) in the USA, and SABRtooth (a multicentre pilot and feasibility study of SABR vs surgery in patients with peripheral stage I NSCLC thought to be at increased risk of complications from surgical resection; Franks K, personal communication) in the UK. Both involve an initial approach to eligible patients by a more neutral initial approach to eligible patients by a more neutral party consisting of a pulmonologist and research nurse or a multidisciplinary management team. This approach
might reduce the bias that could be introduced if the patient is initially seen by either a surgeon or radiation oncologist.

In summary, SABR is better tolerated—and might lead to better overall survival—than surgery for operable clinical stage I NSCLC. These findings justify a larger randomised clinical trial to investigate the superiority of SABR for such patients. Physicians should interpret these findings as confirmation of at least clinical equipoise between SABR and surgical options and should consider SABR as an option for treatment of operable stage I NSCLC.

Contributors

JYC, SS, EFS, and JAR designed the studies, collected, analysed, and interpreted data, and wrote the Article. All other authors participated in the studies, collected, analysed, and interpreted data, and reviewed the Article.

Declaration of interests

JYC has received travel sponsorship from Accuray and Varian Medical Systems, and grants from Varian Medical Systems. SS has received grants and personal fees from Varian Medical Systems. DAB has received grants and personal fees from Varian Medical Systems, and grants from Varian Medical Systems. OD was an employee of Accuray, as senior vice-president of medical affairs, from April, 2006, to December, 2012, during the design and conduct of the STARS trial. BJS has received grants and personal fees from Varian Medical Systems and personal fees from BrainLab AG. JAR has received grants from Varian Medical Systems. All other authors declare no competing interests.

Acknowledgments

We thank all STARS and ROSEL investigators (listed in appendix) who contributed to the preparation of this manuscript. We thank Christine Wogan for editorial assistance. This research was supported by Accuray Inc (NCT00840749), a grant from the Netherlands Organisation for Health Research and Development (ZonMW project number 80-82310-98-08005), NCI Cancer Center Support Grant (Core Grant) CA05672, and NCI Clinical and Translational Science Award U1U RR024148 to MD Anderson Cancer Center.

References


