10-1-2015

A Phase 3 Trial of 2 Years of Androgen Suppression and Radiation Therapy With or Without Adjuvant Chemotherapy for High-Risk Prostate Cancer: Final Results of Radiation Therapy Oncology Group Phase 3 Randomized Trial NRG Oncology RTOG 9902.

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Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2015 October 1; 93(2): 294–302. doi:10.1016/j.ijrobp.2015.05.024.

A Phase III trial of 2 Years of Androgen Suppression (AS) and Radiation Therapy (RT) with or without Adjuvant Chemotherapy (CT) for High-Risk Prostate Cancer: Final Results of Radiation Therapy Oncology Group (RTOG) Phase III Randomized Trial NRG Oncology RTOG 9902

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Conflict of interest: Dr. Dobelbower reports reimbursed costs of per-capita patient enrollment and pathology reimbursement from RTOG. Dr. Shipley reports ownership of Pfizer stock. Dr. Hamstra reports personal fees from Varian, personal fees from Augmenix, personal fees from Medivation, personal fees from Myriad, grants from Novartis, outside the submitted work. Dr. Sandler reports personal fees from AstraZeneca, personal fees from Medivation, grants from Myriad, from Janssen, personal fees from Blue Earth Diagnostics, personal fees from Ferring, personal fees from Bayer, personal fees from eviti, outside the submitted work. Dr. Gomella reports personal fees from Janssen, personal fees from Astellas, personal fees from Bayer, personal fees from Dendreon, outside the submitted work.

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Abstract

Purpose—Long-term (LT) androgen suppression (AS) with RT is a standard treatment for high-risk, localized prostate cancer (PCa). RTOG 9902 was a randomized trial testing the hypothesis that adjuvant combination chemotherapy (CT) with paclitaxel, estramustine, and oral etoposide (TEE) + LT AS+ RT would improve overall survival (OS).

Materials and Methods—High-Risk PCa patients (PSA 20–100 and Gleason score (GS) ≥7 or clinical stage ≥T2 and GS ≥8) were randomized to RT and AS (AS+RT) alone or with adjuvant CT (AS+RT+CT). CT was four 21-day (d) cycles, delivered beginning 28d after 70.2 Gy RT. AS was: LHRH for 24 months (mo) beginning 2 mo prior to RT plus oral anti-androgen for 4 mo before and during RT. The study was designed based on a 6% improvement in OS from 79% to 85% at 5 years, with 90% power and a 2-sided alpha of 0.05.

Results—397 patients (380 eligible) were randomized. The patients had high-risk PCa, 68% having Gleason Score 8–10, and 34% T3–T4 tumors, and median PSA of 22.6 ng/ml. Median follow-up is 9.2 years. The trial closed early because of excess thromboembolic toxicity in the CT arm. 10-year results for all randomized patients revealed no significant difference in AS+RT vs. AS+RT+CT in OS (65% vs. 63%; p=0.81); Biochemical Failure (BF) (58% vs. 54%; p=0.82); Local Progression (LP) (11% vs. 7%; p=0.09); Distant Metastases (DM) (16% vs. 14%; p=0.42); or Disease-Free Survival (DFS) (22% vs. 26%; p=0.61).

Conclusions—NRG Oncology RTOG 9902 showed no significant difference in OS, BF, LP, DM, or DFS with the addition of adjuvant CT to LT AS + RT. The trial provides valuable data regarding the natural history of high-risk PCa treated with LT AS + RT, and has implications for the feasibility of clinical trial accrual and tolerability utilizing CT in PCa.

Introduction

Prostate cancer is the most common malignancy in men, and the second most common cause of male cancer death in the US.[1] Although prostate cancer specific mortality is low in studies of low and intermediate risk prostate cancer patients[2,3] there is significant mortality for men with high-risk prostate cancer.[4]

The Radiation Therapy Oncology Group (RTOG) has studied the strategy of combining androgen suppression (AS) with radiation therapy (RT). In RTOG 8531, the 10 year disease-free survival (DFS) rate for patients treated with RT alone was only 9%, and was significantly improved with the addition of AS.[5] Trials from the European Organization for Research and Treatment of Cancer (EORTC) showed improved survival for poor prognosis prostate cancer patients treated with AS+RT vs. patients treated with RT alone.[6,7]

RTOG 9202 compared a short term regimen AS (2 mo prior to RT and then 2 mo concurrent with RT) with the same regimen followed by long-term (LT, 2 years) AS following RT. For the subset of patients with Gleason Score 8–10 cancers, there was a significant overall survival (OS) benefit noted for LT AS + RT. For patients treated on the LT AS + RT arm of RTOG 9202, the overall biochemical failure rate was 52%, and DFS was 23%, indicating room for further therapeutic improvement[8,9] Bolla et al. from the EORTC also demonstrated that a regimen of 3 years of AS + RT resulted in improved survival when compared with 6 months of AS + RT.[10]

Risk stratification models were developed which used pre-treatment variables such as PSA, Gleason Score, and clinical tumor (T) stage to identify patients who were high-risk for recurrence.[11] Based on these models, in RTOG 9902, a group of high risk patients was identified to test the hypothesis that more intensive treatment upfront, employing cytotoxic chemotherapy (CT), could reduce the number of patients who recurred and result in improved survival when compared with AS and RT alone. Clones which were resistant to initial treatment with AS and RT could be potentially eradicated by CT. CT was to be delivered as an adjuvant following RT. A combination of paclitaxel, estramustine and oral etoposide (TEE), which had shown promise in Phase II studies, was selected as the CT regimen.[12] The primary objective of the trial was to determine if the addition of CT to LT AS + RT would result in improved OS compared with LT AS + RT only.

Materials and Methods

Patient Population

Patients eligible for inclusion on RTOG 9902 were men with high risk, but clinically and radiographically non-metastatic prostate cancer. Eligibility criteria included histologically confirmed prostate cancer with PSA 20–100 ng/ml and Gleason Score (GS) ≥ 7 with any T-Stage, or clinical T-Stage ≥T2 and GS 8–10 with any PSA≤100. Patients were required to have negative lymph nodes by CT or MR, and no evidence of distant metastasis. Patients with imaging positive LN were to be confirmed negative by biopsy. Bone scan was required prior to entry. Baseline PSA, testosterone, hematologic, liver, and renal function studies were required. Zubrod performance status was 0–1. No prior pelvic RT or orchiectomy was allowed. Prior AS was allowed only if started no greater than 30 days prior to protocol entry. Medical oncology consultation was required prior to protocol entry to ensure that patients would be suitable candidates if randomized to chemotherapy. Institutional Review Board (IRB) was obtained at each participating center.

Patients were followed during the first 2 years of treatment with PSA and other laboratory values every 3 months and then every 6 months for 3 years and annually thereafter. Patients

were followed weekly during the course of radiation therapy, and were reassessed prior to each cycle of chemotherapy.

Treatment Schema

All patients were treated with LT (two years) androgen suppression (AS) and RT. AS and RT were identical on both arms. Patients were randomized to receive long-term AS and RT alone (AS+RT) or to receive long-term AS, RT, and 4 cycles of chemotherapy (CT) with paclitaxel, estramustine, and oral etoposide (TEE) (*vide infra*) starting 28 days after conclusion of RT (AS+RT+CT).

Radiation Therapy

RT was started 8 weeks after initiation of AS therapy. Megavoltage equipment with photon energies ≥ 6 MV was utilized. CT treatment planning was recommended. All patients on both arms received pelvic RT. A dose of 46.8 Gy in 1.8 Gy fractions was utilized to treat the prostate and regional lymphatic volumes followed by a prostate boost to deliver 23.4 Gy in 1.8 Gy fractions to bring the total prostate dose to 70.2 Gy. Based on concerns regarding potential bone marrow and gastrointestinal (GI) toxicities, investigators had the option to place the superior border of the pelvic lymph node volumes as low as the bottom of the sacroiliac (SI) joints. If the seminal vesicles (SV) were involved, an intermediate volume including the prostate + SV was treated to 55.8 Gy.

Androgen Suppression Therapy

Prior to the initiation of RT, all patients were treated with total androgen suppression (TAS), including an oral non-steroidal anti-androgen (either bicalutamide 50 mg once a day, or flutamide 250 mg three times a day), in addition to LHRH agonists (leuprolide or goserelin), consistent with design of other RTOG trials of that era.[2, 3, 8] The non-steroidal anti-androgen was discontinued at the end of RT. All patients continued to receive LHRH agonists for a total of 24 months of AS.

Chemotherapy

Patients on AS+RT+CT were randomized to receive 4 cycles of chemotherapy with paclitaxel, estramustine, and oral etoposide [TEE] beginning 28 days following completion of RT. The regimen included: 1) oral estramustine 280 mg three times a day for the first 14 of every 21 days, 2) oral etoposide 50 mg/m^2 in divided doses twice a day for the first 14 of every 21 days, and 3) paclitaxel 135 mg/ m^2 intravenously over 1 hour on day 2 of each 21 day cycle. In addition, after June 3, 2002, the protocol was amended to require anticoagulation with warfarin to keep the International Normalized Ratio (INR) >1.5 and < 2.5. The protocol specified dose modifications with respect to patients with impaired renal function and reduced platelet and white blood cell counts.

Statistical Design

The primary endpoint was overall survival (OS), defined as death due to any cause and measured from randomization to date of death. Patients were stratified by PSA (≤ 10 vs > 10 to ≤ 100), tumor stage (T1–2 vs T3–4), Gleason Score (7 vs 8–10), and prior hormones (no

vs yes) and then randomized 1:1 to AS+RT or AS+RT+CT using a permuted block randomization scheme as defined by Zelen.[13] The primary hypothesis was that the addition of CT to RTAS would increase OS, corresponding to a 6% improvement at 5 years from 79% to 85% (Hazard ratio [HR] = 0.67). Using a group sequential design, the original target sample size was 1440 patients, in order to provide the required 340 OS events to detect the hypothesized increase, with 90% power, a 2-sided significance level of 0.05, and three planned interim analyses of efficacy. A toxicity monitoring rule was included to test for an unacceptably high toxicity rate of grade 3+ acute toxicity on the AS+RT+CT arm. Based on earlier chemotherapy studies, the hypothesized rate was 20%, with the test designed to test for a 20% increase to 40%, which would be considered unacceptable. Two-hundred and sixty-two patients were required on the AS+RT+CT arm to test this hypothesis, with a significance level of 0.025, 90% power, and three interim analyses.

Statistical Methods

All analyses were performed using SAS version 9.2 statistical software (SAS Institute Inc, Cary, North Carolina). Secondary endpoints included biochemical failure (BF), using the ASTRO definition; local progression (LP), failure – documented clinical local and/or regional progression; distant metastases (DM), failure – appearance of distant metastases; disease-free survival (DFS), failure – BF, LP, DM, or death due to any cause. All endpoints were measured from the date of randomization to first failure or last follow-up for non-failures. Chemotherapy, hormone therapy, and acute radiotherapy toxicities were graded using the CTC version 2.0. Late radiotherapy toxicities were graded using the RTOG/EORTC Late Toxicity Criteria. The Kaplan-Meier[14] approach was used to estimate OS and DFS and the log-rank test[15] was used to compare treatment arms. Cumulative incidence[16] was used to estimate BF, LP, and DM and the Gray's test[17] was used to compare treatment arms. Death was considered a competing risk for BF, LP, and DM. Univariate and multivariate Cox proportional hazard models[18] were used to obtain hazard ratios (HRs) for OS and DFS. Univariate and multivariate Fine-Gray regression models[19] were used to obtain HRs for BF, LP, and DM. Treatment is coded such that a hazard ratio (HR) > 1 indicates an increased risk of failure for the AS+RT+CT arm.

Results

The trial opened on January 11, 2000, and closed on October 4, 2004, with a total of 397 of the 1440 planned patients entered and randomized: 197 in the AS+RT arm and 200 in the AS+RT+CT arm. Of the 397 patients randomized, 17 did not meet the eligibility criteria, 8 on AS+RT, and 9 on AS+RT+CT. The primary reasons for ineligibility were hormonal therapy started > 30 days prior to study entry, and pre-randomization labs not done (Figure 1: Consort Diagram). The results are reported for all randomized patients, as specified in the protocol. All eligible patients were also analyzed, per the protocol, with similar results, not reported here. The pretreatment characteristics for all randomized patients are presented in Table 1. The treatment arms were well balanced. Median age was 66 years (min-max: 42–81), median PSA was 22.6 ng/ml (min-max: 0.1–96.4). Sixty-eight percent of patients had GS 8–10, 34% were clinical stage T3-T4, and 72% of patients had intercurrent disease.

Intercurrent disease included cardiovascular, hypertension, and diabetes. Hypertension was the most common.

Accrual to the trial was suspended from April 23, 2002 to June 3, 2002 after the RTOG Data Monitoring Committee (DMC) noted an excess of thromboembolic events, and reopened after the protocol was modified to include anti-coagulation with warfarin during TEE therapy. At that time, a revised monitoring schedule was included based on the rate of grade 2+ thromboembolic events on the AS+RT+CT arm; a 5% observed rate was hypothesized, with the study designed to detect an unacceptable rate of 23%, requiring 30 total patients to test and in three stages; if 3 or more patients experienced unacceptable thromboembolic toxicity, then the CT regimen would be deemed unacceptable. Subsequently additional thromboembolic events were noted, and the DMC suspended accrual to the protocol on July 30, 2004, which permanently closed to accrual October 4, 2004. The use of estramustine was believed to have contributed to the thromboembolic toxicity. Toxicity results were evaluated for all 380 eligible patients. Detailed early toxicity results for the trial have been previously reported.[20] There were three grade 5 toxicities noted on AS+RT+CT. There were two cases of death from infection/febrile neutropenia, and one case of death from acute myelogenous leukemia (AML) 77 months after randomization. With long-term follow-up, there was no excess in late RT toxicity associated with AS+RT+CT arm. Toxicity results for randomized patients are summarized in Table 2.

With a median follow-up for all patients of 9.2 years (min-max: 0.4–13.3), 152 of the 340 primary endpoint events (deaths) per the original statistical design have occurred as of this report. 10.0 years is the median follow-up for surviving patients. This corresponds to 62% statistical power to detect the hypothesized increase in OS, as compared to the 90% statistical power per the original statistical design. There were no statistically significant differences noted in any of the pre-specified endpoints of OS, BF, LP, DM, or DFS. A summary of 5 and 10-year outcome results for all randomized patients is presented in Table 3. Ten-year results for all randomized patients by treatment arms (AS+RT vs AS+RT+CT) were 65% vs. 63% for OS (Figure 2), 58% vs. 54% for BF (online: Figure A), 11% vs. 7% for LP (online: Figure B), 16% vs. 14% for DM (online: Figure C), and 22% vs. 26% for DFS (online: Figure D). First failure was BF for 68% of patients, LP for 3% of patients, DM for 5% of patients, and death related to protocol treatment for 1% of patients. The bulk of failures occurred within 4.5 years of randomization (75%) (online: Table A) and 26% of patients had prostate cancer reported as cause of death (online: Table B). The primary causes of non-prostate cancer death were cardiovascular or respiratory event (50%) and lung cancer (21%). Multivariate analysis revealed that only age, prior hormonal therapy (HT), and the presence of intercurrent disease were associated with OS. The significance of prior HT is not certain, as subsequent events may have been time shifted as endpoints were calculated from the dates of randomization, not the dates of initiation of HT. Treatment arm, PSA, GS, and tumor stage were not significant (Table 4).

Many patients did not complete the chemotherapy, or even start chemotherapy, because of toxicity or because of the premature closure of the study. Therefore, a *post hoc* analysis regarding the outcomes with respect to the amount of chemotherapy received was performed. Of the 200 randomized patients assigned to the chemotherapy arm, 51 (25.5%)

received no chemotherapy, 67 (33.5%) received partial chemotherapy (1–3 cycles), and 82 (41%) received all four cycles of chemotherapy. RT was delivered per protocol or with acceptable variation for 92% of randomized patients. When the patients who received partial chemotherapy, and the patients who received all four cycles of chemotherapy were compared to the control group, there was no significant difference noted in OS, BF, LP, DM, or DFS (online: Tables C and D).

Discussion

There were no significant differences noted in OS or in the other pre-specified endpoints of BF, LP, DM, or DFS. There was a difference in toxicity, which resulted in premature closure of the study. With the sample size of 397 patients, there was no difference noted for any of the endpoints, and no difference noted when the subgroup who received the four cycles of chemotherapy was compared to control. Multivariate analysis did not suggest that there was a benefit of the trial therapy after controlling for tumor stage, Gleason Score, and pre-treatment PSA in the model.

Although the trial was negative, this was the first large multicenter randomized phase III trial incorporating chemotherapy into the management of non-localized prostate cancer treated with RT. There had been skepticism about the ability to accrue patients to a trial where non-metastatic patients would be randomized to treatment with CT. The accrual of 397 patients in the approximately 4 years RTOG 9902 was open demonstrated the feasibility of such a trial.

Why was the trial negative? There is a caveat because of the smaller than planned sample size, due to the early closure, which reduced the ability to detect the hypothesized difference between the treatment arms. All cancer treatment regimens have to balance the therapeutic ratio of efficacy over toxicity. In the case of RTOG 9902, there was excess toxicity noted with the chemotherapy regimen, with treatment associated mortality. In addition, the chemotherapy regimen (TEE) utilized may not have been sufficiently active to have produced the initially projected difference in outcomes.

Improvements in systemic therapy options for prostate cancer have occurred since 1999. The TEE regimen used in RTOG 9902 would currently be regarded as obsolete. At that time, systemic therapy options for patients outside of androgen suppression were limited. In 1999, no chemotherapy agents had been demonstrated to result in improved survival for patients with hormone refractory prostate cancer. In 2004 docetaxel (Taxotere), was demonstrated to improve survival for these patients. The successor trial to RTOG 9902, RTOG 0521, employed a similar schema to RTOG 9902, but utilized docetaxel rather than TEE as the chemotherapeutic regimen.

RTOG 0521 also updated RT doses and techniques compared with RTOG 9902. There have been advances in RT delivery since the trial was designed in 1999. The dose of RT in RTOG 9902 was 70.2 Gy. Since the trial was designed in 1999, dose escalation in RT has permitted an increase in the doses of RT typically utilized.[21] Atlases for more consistent definition of nodal volumes have also been devised.[22] It is possible that with contemporary RT doses,

target definition, and delivery techniques, that any difference in treatment outcomes due to improved systemic therapy could become more apparent. With the use of docetaxel rather than TEE and the use of updated RT doses and techniques, RTOG 0521 completed targeted accrual in 2009 with 612 patients. The trial did not require early closure because of toxicity. Reporting of 0521 results remains pending.[4]

The RTOG 9902 trial also helped to provide a database which better defines the natural history of high risk prostate cancer treated with LT AS + RT. Age and intercurrent disease were identified as significant factors prognostic for overall survival, and as noted previously, treatment assignment was not a significant factor. For the control group 10-year data showing 65% OS, 22% DFS, 58% BF, 11% LP, and 16% DM can serve as useful benchmarks in considering future treatment regimens. Although the majority of recurrences occurred in the first 4.5 years, there remains a continued rate of treatment failure after that interval.

The RTOG 9902 trial, when compared with the contemporaneous RTOG 9910 trial, which focused on intermediate risk patients, confirms the validity of RTOG risk stratification between high and intermediate risk. The studies had been designed so that there would be no overlap in eligibility criteria between the two trials. In the RTOG 9910 intermediate risk prostate cancer trial, there was no difference in prostate cancer deaths between the two arms (randomized between 16 weeks of AS+ RT and 36 weeks of AS + RT), there were 12% prostate cancer deaths.[3] This compares with 26% prostate cancer deaths noted in RTOG 9902. This suggests that the cohort of patients identified as high risk by RTOG 9902 is indeed a group of patients, who, even with long term AS+ RT, have a significant risk of death from prostate cancer.

Improving OS and other disease-control outcome measures for patients with high-risk but non-metastatic prostate cancer remains an important therapeutic goal. A number of agents have been shown to have activity in metastatic prostate cancer. Integration of these agents with established therapies, such as long term AS + RT, remains a future therapeutic strategy.[23]

Conclusion

RTOG 9902 showed no statistically significant difference in the outcomes of OS, BF, LP, DM, or DFS with the addition of chemotherapy with TEE to a regimen of two years of AS + RT. The study was terminated early because of toxicity, and the attendant reduction in the sample size may have reduced the ability to have determined significant differences between the treatment arms. A subsequent trial, RTOG 0521, completed accrual in 2009 and results are pending. RTOG 0521 used docetaxel rather than TEE therapy, as well as updated RT doses and techniques. This trial and RTOG 0521 will help to define the role of adjuvant chemotherapy in the management of high-risk prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Substantial contribution by non-authors: Kathryn A. Winter, MS; NRG Oncology Statistics and Data Management Center, Director of Statistics and James Concannon, NRG Oncology Publications Committee.

This project was supported by grants RTOG U10CA21661, NRG U10CA180868 and NRG U10CA180822 from the National Cancer Institute (NCI), and by Bristol Myers Squibb and Pfizer.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. CA: A Cancer Journal for Clinicians. 2014; 64:9–29. [PubMed: 24399786]
2. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and Short-term androgen deprivation for localized prostate cancer. N Engl J Med. 2011 Jul 14; 365(2):107–118. [PubMed: 21751904]
3. Pisansky TM, Hunt D, Gomella LG, et al. Duration of Androgen Suppression before Radiotherapy for Localized Prostate Cancer—Radiation Therapy Oncology Group Randomized Trial 9910. J Clin Oncol. 2015; 33:332–339. [PubMed: 25534388]
4. Rosenthal SA, Sandler HM. Treatment Strategies for high-risk locally advanced prostate cancer. Nature Reviews Urol. 2010; 7(1):31–38.
5. Pilepich MV, Winter K, Lawton CA, et al. Androgen Suppression Adjuvant to Definitive Radiotherapy in Prostate Carcinoma—Long-term Results of Phase III RTOG 85-31. Int J Radiat Oncol Biol Phys. 2005; 61:1285–1290. [PubMed: 15817329]
6. Bolla M, Gonzalez D, Warde P, et al. Improved Survival in Patients with Locally advanced Prostate Cancer treated with Radiotherapy and Goserelin. N Engl J Med. 1997; 337:295–300. [PubMed: 9233866]
7. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a Phase III randomized trial. Lancet. 2002; 360:103–106. [PubMed: 12126818]
8. Hanks GE, Pajak TF, Porter A, et al. A Phase III Trial of Long Term Adjuvant Androgen Suppression following Neoadjuvant Hormonal Cytoreduction and Radiotherapy in Locally Advanced Carcinoma of the Prostate: The RTOG Protocol 92-02. J Clin Oncol. 2003; 21:3972-397. [PubMed: 14581419]
9. Horwitz EM, Bae K, Hanks GE, Porter A, et al. Ten-Year Follow-up of Radiation Therapy Oncology group Protocol 92-02: A Phase III Trial of the duration of elective Androgen Deprivation in locally advanced prostate cancer. J Clin Oncol. 2008; 26:2497–2504. [PubMed: 18413638]
10. Bolla M, deReijke TM, Van Tienhoven G, Van den Bergh ACM, et al. Duration of Androgen Suppression in the Treatment of Prostate Cancer. N Engl J Med. 2009; 360:2516–2527. [PubMed: 19516032]
11. D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment Nomogram for Prostate-Specific Antigen Recurrence after Radical Prostatectomy or External-Beam Radiation Therapy for Clinically Localized Prostate Cancer. J Clin Oncol. 1999; 17:168–173. [PubMed: 10458230]
12. Smith DC, Esper P, Strawderman M, Redman B, Pienta KJ. Phase II Trial of Oral Estramustine, Oral Etoposide, and Intravenous Paclitaxel in Hormone-Refractory Prostate Cancer. J Clin Oncol. 1999; 17:1664–1671. [PubMed: 10561202]
13. Zelen M. The randomization and stratification of patients to clinical trials. J Chronic Dis. 27(7–8): 365–375. [PubMed: 4612056]
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Stat Assoc. 1958; 53:457–481.
15. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966; 50:163–170. [PubMed: 5910392]
16. Kalbfleisch, JD.; Prentice, RL. The statistical analysis of failure time data. New York: John Wiley & Sons; 1980. p. 167-169.
17. Gray RJ. A class of K-samples test for comparing the cumulative incidence of a competing risk. Ann Statistics. 1988; 16:1141–1154.

18. Cox DR. Regression models and life-tables. Journal of the Royal Statistical Society, Series B. 1972; 34:187–202.
19. Fine J, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. J Am Stat Assoc. 1999; 94:496–509.
20. Rosenthal SA, Bae K, Pienta KJ, Sobczak ML, et al. Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression and radiotherapy versus long-term androgen suppression and radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02. Int J Radiat Oncol Biol Phys. 2009; 73:672–678. [PubMed: 18990504]
21. Kuban DA, Tucker SL, Dong L, Starkschall G, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008; 70:67–74. [PubMed: 17765406]
22. Lawton CA, Michalski JM, El-Naqa I, Kuban DA, et al. Variation in the Definition of Clinical Target Volumes for Pelvic Nodal Conformal Radiation Therapy for Prostate Cancer. Int J. Radiat Oncol Biol Phys. 2009; 74:377–382. [PubMed: 18947941]
23. Sridhar SS, Freedland SJ, Gleave ME, Higano C, Mulders P, Parker C, Sartor O, Saad F. Castration-resistant prostate cancer: from new pathophysiology to new treatment. Eur Urol. 2014 Feb; 65(2):289–299. [PubMed: 23957948]

Summary

NRG Oncology RTOG 99-02 was a 397 patient randomized trial testing the role of adjuvant chemotherapy (CT) in conjunction with long term androgen suppression + radiotherapy for high-risk prostate cancer patients (PCa). With long-term follow-up, there was no significant difference in efficacy endpoints. The trial provides valuable data regarding the natural history of high-risk PCa. RTOG 9902 has implications for the feasibility of clinical trial accrual and tolerability of CT for patients with PCa.

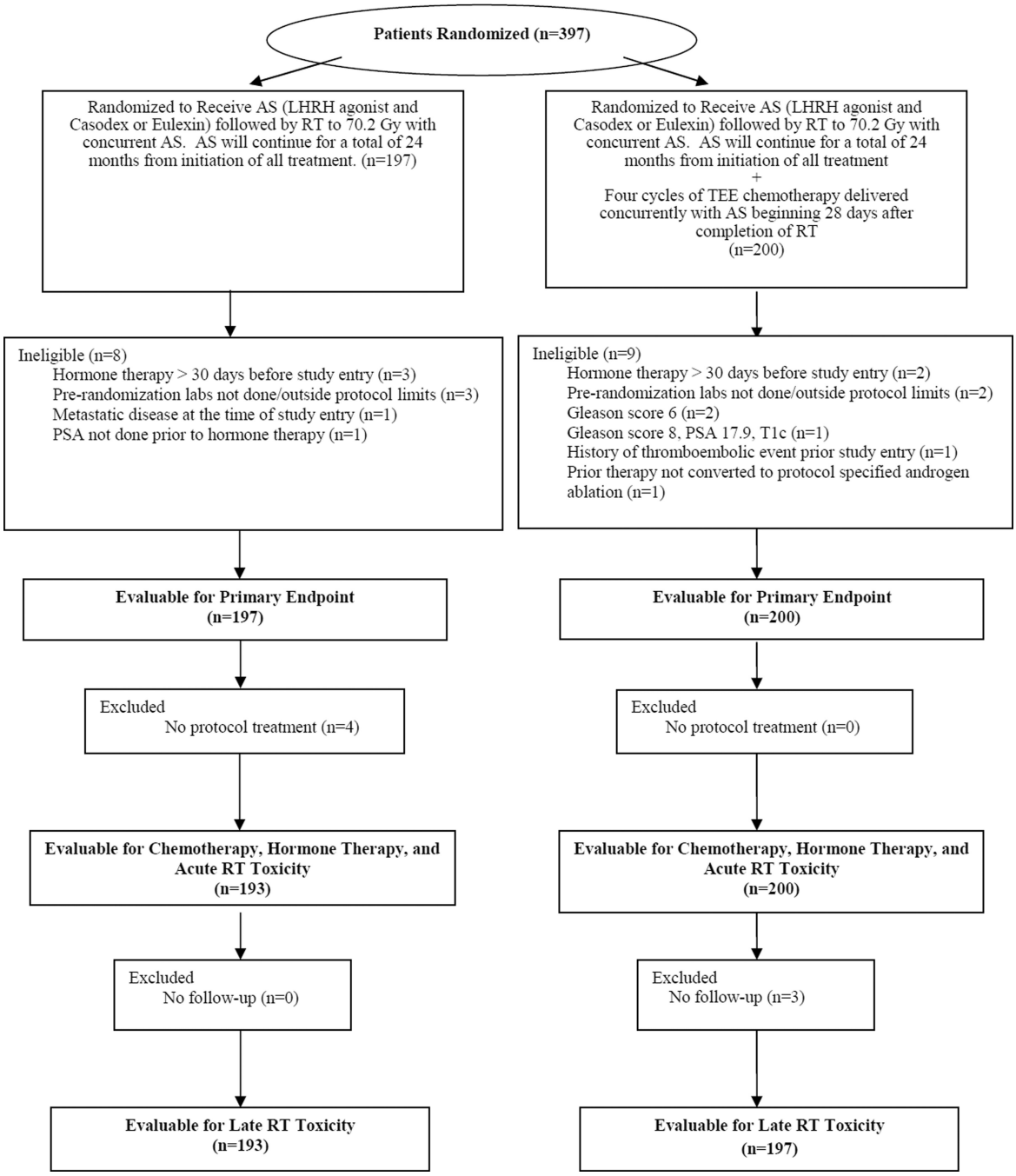

Figure 1.
Consort Diagram

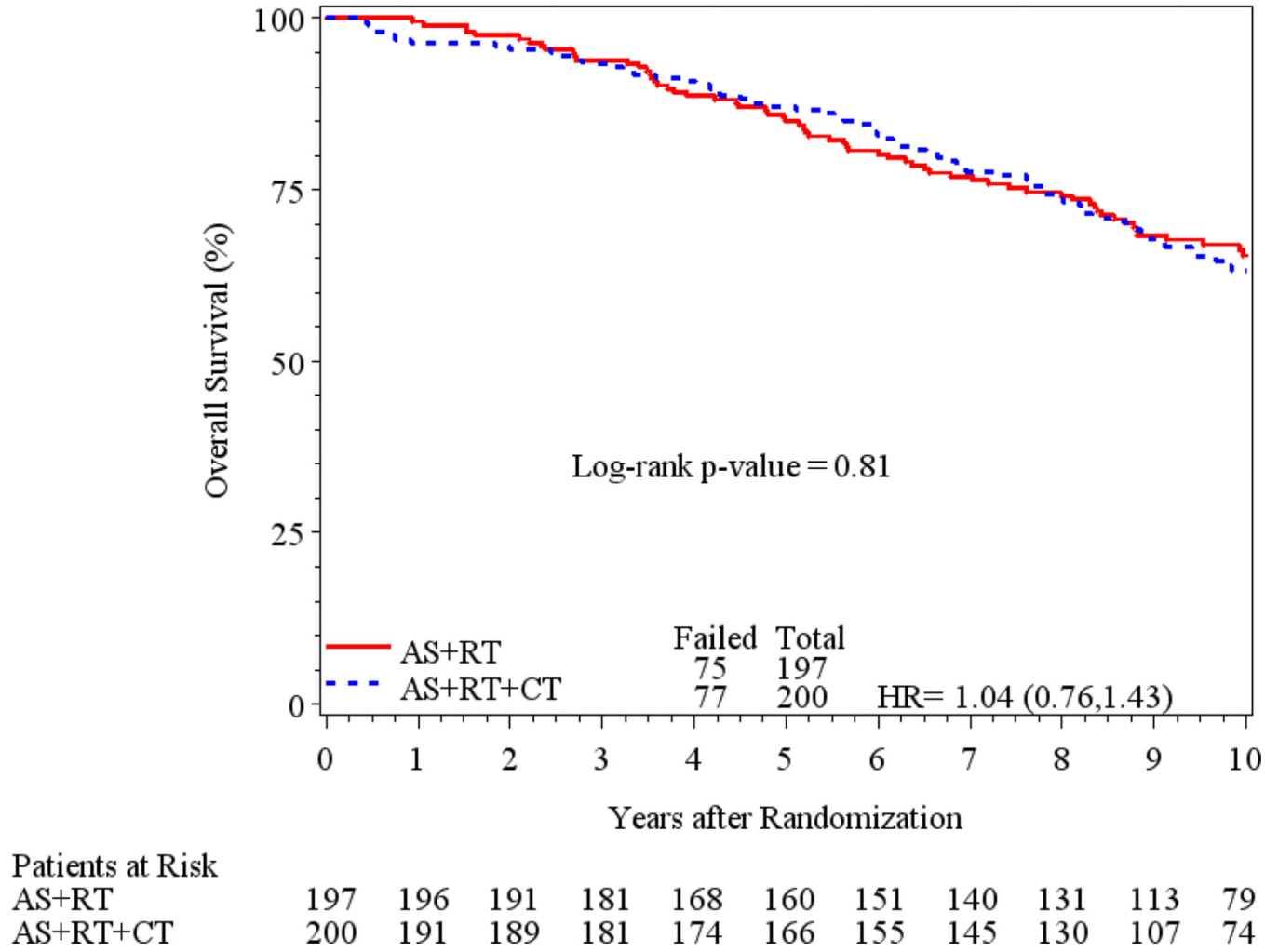

Figure 2.
RTOG 9902: Overall Survival by Treatment Arm: All Randomized patients (n=397)

Table 1

RTOG 9902: Pre-Treatment Characteristics: All Randomized Patients

	AS+RT (n=197)		AS+RT+CT (n=200)		Total (n=397)	
Age (years)						
Median	65		66.5		66	
Min - Max	42 – 79		42 – 81		42 – 81	
Q1 – Q3	59 – 71		61 – 71.5		60 – 71	
PSA (ng/ml)*						
Median	22.5		22.8		22.6	
Min - Max	0.1 – 96.4		1.4 – 95.7		0.1 – 96.4	
Q1 – Q3	9.4 – 39.8		8.9 – 43.6		9.1 – 40.2	
< 10	52	(26.4%)	55	(27.5%)	107	(27.0%)
≥ 10	144	(73.1%)	145	(72.5%)	289	(72.8%)
Unknown	1	(0.5%)	0	(0.0%)	1	(0.3%)
Race						
White	132	(67.0%)	144	(72.0%)	276	(69.5%)
Hispanic	4	(2.0%)	3	(1.5%)	7	(1.8%)
African American	56	(28.4%)	51	(25.5%)	107	(27.0%)
Native Hawaiian or other Pacific Islander	0	(0.0%)	1	(0.5%)	1	(0.3%)
Asian	2	(1.0%)	1	(0.5%)	3	(0.8%)
American Indian or Alaska Native	2	(1.0%)	0	(0.0%)	2	(0.5%)
Unknown	1	(0.5%)	0	(0.0%)	1	(0.3%)
Gleason						
6†	0	(0.0%)	1	(0.5%)	1	(0.3%)
7	63	(32.0%)	64	(32.0%)	127	(32.0%)
8–10	134	(68.0%)	135	(67.5%)	269	(67.8%)
Zubrod Performance Status						
0	173	(87.8%)	183	(91.5%)	356	(89.7%)
1	24	(12.2%)	17	(8.5%)	41	(10.3%)
T-Stage*						
T1 – T2	131	(66.5%)	130	(65.0%)	261	(65.7%)
T3 – T4	66	(33.5%)	70	(35.0%)	136	(34.3%)
Prior Hormones*						
No	89	(45.2%)	88	(44.0%)	177	(44.6%)
Yes	108	(54.8%)	112	(56.0%)	220	(55.4%)
Intercurrent Disease						
Absent	47	(23.9%)	60	(30.0%)	107	(27.0%)
Present	150	(76.1%)	136	(68.0%)	286	(72.0%)
Unknown	0	(0.0%)	4	(2.0%)	4	(1.0%)

*Stratification factor

Q1 = first quartile; Q3 = third quartile

† GS=6 was considered ineligible for this trial.

Table 2

RTOG 9902: Summary of Worst Toxicity per Patient: All Randomized Patients

Type	Toxicity	Grade	AS+RT		AS+RT+CT	
			(n=193)		(n=200)	
Chemotherapy, Hormone Therapy, and Acute Radiotherapy Toxicity (n=393/397[†])	Worst non-hematologic	1	21	(10.9%)	10	(5.0%)
		2	92	(47.7%)	67	(33.5%)
		3	75	(38.9%)	106	(53.0%)
		4	2	(1.0%)	12	(6.0%)
		5	0	(0.0%)	3	(1.5%)
	Worst overall	1	20	(10.4%)	7	(3.5%)
		2	92	(47.7%)	45	(22.5%)
		3	76	(39.4%)	103	(51.5%)
		4	2	(1.0%)	40	(20.0%)
		5	0	(0.0%)	3	(1.5%)
			(n=193)		(n=197)	
Late Radiotherapy Toxicity (n=390/397[‡])	Worst overall	1	64	(33.2%)	56	(28.4%)
		2	49	(25.4%)	50	(25.4%)
		3	12	(6.2%)	17	(8.6%)
		4	0	(0.0%)	3	(1.5%)
		5	0	(0.0%)	0	(0.0%)

[†]Toxicities were graded with CTC version 2.0; excludes 4 patients who did not receive protocol treatment.

[‡]Toxicities were graded with RTOG/EORTC late toxicity criteria; excludes 4 patients who did not receive protocol treatment and 3 patients who did not have late RT toxicity information.

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2016 October 01.

Table 3

RTOG 9902: Overall Survival, Biochemical Failure, Local Progression, Distant Metastasis, and Disease-Free Survival Rates by Treatment Arm: All Randomized Patients (n=397)

Endpoint	RX Arm	n	Events	5-year Estimate, % (95% CI)	10-year Estimate, % (95% CI)	p-value*	HR ($\lambda_{AS+RT+CT}/\lambda_{AS+RT}$)† (95% CI)
OS	AS+RT	197	75	84.9 (79.9, 90.0)	65.4 (58.4, 72.4)	0.81	1.04 (0.76,1.43)
	AS+RT+CT	200	77	87.2 (82.4, 91.9)	63.1 (55.9, 70.2)		
BF	AS+RT	197	110	48.0 (40.7, 54.8)	57.5 (50.0, 64.2)	0.82	0.97 (0.74,1.27)
	AS+RT+CT	200	106	47.9 (40.7, 54.8)	53.9 (46.5, 60.6)		
LP	AS+RT	197	23	5.8 (3.1, 9.7)	11.2 (7.2, 16.2)	0.09	0.56 (0.28,1.10)
	AS+RT+CT	200	13	4.1 (1.9, 7.6)	7.1 (3.9, 11.5)		
DM	AS+RT	197	31	10.4 (6.6, 15.2)	16.0 (11.1, 21.7)	0.42	0.81 (0.48,1.36)
	AS+RT+CT	200	26	8.3 (4.9, 12.7)	13.5 (9.0, 19.0)		
DFS	AS+RT	197	150	39.1 (32.2, 46.0)	22.2 (16.2, 28.3)	0.61	0.94 (0.75,1.19)
	AS+RT+CT	200	145	42.9 (35.9, 49.9)	25.8 (19.4, 32.2)		

Abbreviations: RX, treatment; n, number; CI, confidence interval; HR, hazard ratio

*Log-rank test for OS & DFS; Gray's test for BF, LP, DM

†Cox proportional hazards models for OS & DFS; Fine-Gray regression models for BF, LP, DM

Table 4

RTOG 9902: Overall Survival: Multivariate Analysis: All Randomized Patients (n=397)

Adjustment Variables*	Comparison	Adjusted HR** (95% CI)	p-value‡
Assigned treatment	AS+RT+CT vs. AS+RT	1.06 (0.77, 1.47)	0.71
Prior Hormones	Yes vs. No	1.47 (1.06, 2.05)	0.023
Intercurrent Disease	Present/unknown vs. Absent	1.59 (1.06, 2.38)	0.026
PSA (ng/ml)	≥ 10 vs. < 10	0.85 (0.58, 1.25)	0.42
Gleason score	8–10 vs. 6–7	0.99 (0.67, 1.48)	0.98
Tumor stage	T3–T4 vs. T1–T2	1.21 (0.87, 1.69)	0.26
Age (years)	Continuous (unit increase = 5)	1.22† (1.09, 1.37)	0.0007

*All clinically relevant variables were included in the model along with assigned treatment.

**Hazard Ratio: a hazard ratio of 1 indicates no difference between the two subgroups. The variables were coded such that a HR > 1 indicates an increased risk of death for the first level of the variables listed.

†Interpretation: An increase of 5 years in age corresponds to a 22% increase in the risk of dying.

‡p-value from Chi-square test using the Cox proportional hazards model