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Analysis of the Correlation between Endorectal MRI Response to Neoadjuvant Chemotherapy and Biochemical Recurrence in Patients with High-Risk Localized Prostate Cancer

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Abstract

Background—Intermediate endpoints are desirable to expedite the integration of neoadjuvant systemic therapy into the treatment strategy for high-risk localized prostate cancer. Endorectal MRI at 1.5 Tesla (1.5T erMRI) response has been utilized as an endpoint in neoadjuvant trials but has not been correlated with clinical outcomes.

Methods—Data were pooled from two trials exploring neoadjuvant chemotherapy in high-risk localized prostate cancer. Trial 1 explored docetaxel for 6 months and Trial 2 explored docetaxel plus bevacizumab for 4.5 months, both prior to radical prostatectomy. erMRI was done at baseline and end of chemotherapy. 1.5T erMRI response, based upon T2W sequences, was recorded. Multivariable Cox regression was undertaken to evaluate the association between clinical parameters and biochemical recurrence.

Results—There were 53 evaluable patients in the combined analysis: 20 (33%) achieved a PSA response, 16 (27%) achieved an erMRI partial response, and 24 (40%) achieved an erMRI minor response. Median follow-up was 4.2 years and 33 of 53 evaluable (62%) patients developed biochemical recurrence. On multivariable analysis, PSA response did not correlate with biochemical recurrence (HR=0.58, 95% CI 0.25–1.33) and paradoxically erMRI response was associated with a significantly shorter time to biochemical recurrence (HR=2.47, 95% CI 1.00–6.13).

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Conflicts of Interest
Galsky – Served as a consultant to Dendreon, Jannsen, Astellas, Glaxo Smith Kline
Xie - none
Nakabayashi - none
Ross - none
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Taplin – Served as a consultant to Sanofi, Medivation, Jannsen, Dendreon, Tokai
Oh - none

Conclusions—Response by 1.5T erMRI does not correlate with a decreased likelihood of biochemical recurrence in patients with high-risk localized prostate cancer treated with neoadjuvant docetaxel and may be associated with inferior outcomes. These data do not support the use of 1.5T erMRI response as a primary endpoint in neoadjuvant chemotherapy trials.

Keywords

Prostate cancer; neoadjuvant chemotherapy; endorectal MRI; intermediate endpoints

Introduction

Prostate cancer is the most common cancer diagnosed in men in the United States. [1] In the "prostate-specific antigen (PSA)-era", the vast majority of patients with prostate cancer present with clinically localized disease and are cured with surgery or radiation, or may even be safely monitored without immediate intervention on surveillance protocols. [2–3] However, a subset of men with clinically localized prostate cancer harbor micrometastases, and ultimately relapse despite local therapy, contributing to over 30,000 prostate cancer deaths per year in the United States alone. [1] Clinico-pathologic features have been identified that may be utilized to identify this high-risk group of men. [4–7] Thus, several groups have explored the integration of neoadjuvant chemotherapy, prior to radical prostatectomy, in an attempt to improve the outcomes of these patients. [8–10]

Intermediate endpoints, events or biomarkers that are early precursors to a given health outcome, are highly desirable in expediting the development of neoadjuvant approaches in prostate cancer. Intermediate endpoints need not necessarily fulfill the statistical criteria for "surrogacy" [11] to be useful in screening the activity of novel therapies and prioritizing regimens for further testing. Such endpoints, when applied in the phase II setting, can help inform critical decisions regarding the initiation of large and expensive definitive phase III trials. Though complete pathologic response has served as an important intermediate endpoint in phase II neoadjuvant trials in other solid tumors [12], pathologic complete responses have historically been rarely achieved in prostate cancer. Alternatively, most patients with high-risk localized prostate cancer have an elevated serum PSA, and measurable tumor lesions on erMRI, and post-treatment changes in these variables can be readily assessed.

We have previously completed sequential trials of neoadjuvant docetaxel-based chemotherapy prior to radical prostatectomy in patients with high-risk localized prostate cancer. [10, 13] Both trials integrated baseline and post-treatment erMRI measurements prospectively as an endpoint. In the current analysis, we have explored the prognostic significance of post-treatment changes in erMRI measurements and PSA, to generate further support for the use of these parameters as intermediate endpoints in future neoadjuvant trials.

Patients and methods

Patient Population

Data from two prospective phase II trials of docetaxel-based neoadjuvant chemotherapy administered prior to radical prostatectomy in patients with high-risk clinically localized prostate cancer were pooled for the current analysis. The full details of both trials have previously been published. [10, 13] Trial 1 evaluated docetaxel 36 mg/m^2 administered weekly for 6 months prior to radical prostatectomy. Trial 2 evaluated docetaxel 70 mg/m^2 plus bevacizumab 15 mg/kg every 3 weeks for 4.5 months (6 cycles; bevacizumab omitted for cycle 6) prior to radical prostatectomy. The inclusion criteria defining high-risk disease were similar in the two trials. Patients eligible for Trial 1 had at least one of the following characteristics: (a) clinical stage T3 disease; (b) serum PSA > 20 ng/mL; (c) Gleason score ≥ 8; or (d) Gleason score of 7 with a predominant component of 4, with either seminal vesicle involvement on erMRI and/or >5 positive core biopsies involved with cancer. Patients eligible for Trial 2 had at least one of the following characteristics: (a) clinical stage T3 disease, (b) serum PSA > 20 ng/mL, (c) Gleason score ≥ 8, (c) Gleason score of 7 and erMRI T3 disease, or (d) PSA velocity of ≥ 2 ng/mL/y in the year before diagnosis. All patients were required to be free from evidence of metastatic disease, have an Eastern Cooperative Oncology Group performance status of 0 to 1, and have a serum testosterone of >100 ng/dL. Both trials were approved by the Institutional Review Boards at all participating institutions. All patients provided written informed consent prior to trial enrollment.

Outcome Assessments

Patients enrolled on Trial 1 underwent an erMRI at baseline and after 2 months of therapy. Provided there was no evidence of disease progression on T2W sequences, patients continued on treatment and underwent a repeat erMRI after completion of neoadjuvant chemotherapy (approximately 6 months after initiation of chemotherapy). On Trial 2, patients underwent an erMRI at baseline and again after completing 6 cycles of neoadjuvant chemotherapy (approximately 4.5 months after initiation of chemotherapy).

Tumor size was calculated as follows: On the baseline erMRI, one target prostate cancer lesion was identified. This lesion was identified on multiplanar T2 weighted imaging. The target lesion was identified as the largest of the lesions in the prostate and was ideally > 0.5 mm^3. The target lesion was measured and recorded by its longest diameter in 3 dimensions to derive a volumetric measurement. Two independent radiologists centrally reviewed all erMRIs, blinded to clinical outcome, on Trial 1. On Trial 2, 36/41 patients enrolled (all patients at Dana Farber Cancer Center) had erMRIs reviewed by a single study radiologist, blinded to clinical outcome.

On Trial 1, serum PSA measurements were obtained at baseline and monthly during neoadjuvant chemotherapy. On Trial 2, serum PSA measurements were obtained at baseline and on day 1 of each neoadjuvant chemotherapy cycle (every 3 weeks).

Statistical Design

This primary objective of this analysis was to evaluate the association between erMRI response and clinical outcome (biochemical recurrence), in patients with high-risk localized prostate cancer treated with docetaxel-based neoadjuvant therapy. Only patients that underwent radial prostatectomy were included in the analysis.

erMRI response was categorized as a partial response (PR; >50% decline for the largest lesion during chemotherapy), a minor response (MR; 25%–50% decline), or no response. PSA response was defined as >50% decline in PSA compared to baseline. Biochemical recurrence was defined as the first PSA ≥ 0.2ng/mL (confirmed by subsequent PSA ≥ 0.2) or date of initiation of new therapy (including salvage RT or hormonal therapy) post-radical prostatectomy. Patients without evidence of biochemical recurrence were censored at last follow-up for disease. Overall survival was defined as the time from date of surgery until date of death or last follow-up for survival.

Fisher Exact test was used to evaluate the association between erMRI and PSA response. The distribution and median time to biochemical recurrence were estimated using the Kaplan-Meier methodology; comparison between groups was conducted using the log-rank test or a stratified log-rank test. Hazard ratios and 95% confidence intervals (CI) were estimated from Cox regression and Wald Chi-Square tests were reported. Multivariable Cox regression was also undertaken to adjust for patient and disease characteristics in the comparison of erMRI response.

Results

Patient, Treatment, and Tumor Characteristics

The patient characteristics are outlined in Table 1. Trial 1 enrolled 19 patients between January 2000 to October 2001 and Trial 2 enrolled 41 patients between July 2006 and November 2008. The baseline patient characteristics on both trials were similar, though Trial 2 enrolled a higher proportion of patients with cT3 or Gleason ≥ 8 tumors. Patients on Trial 1 completed a median of 5.3 months of neoadjuvant chemotherapy while patients on Trial 2 completed a median of 4.1 months of neoadjuvant chemotherapy. Three patients on Trial 1 and 4 patients on Trial 2 did not undergo radical prostatectomy. The reasons that patients did not undergo radical prostatectomy, and the number of patients with unevaluable erMRI and/or PSA data, are detailed in Figure 1.

erMRI and PSA Responses

The PSA and erMRI response proportions are detailed in Table 2. The erMRI response rate (PR+MR) was 67% in patients who did not achieve a PSA response and was 70% in PSA responders (p=0.99). In Trial 1, PSA responders had a lower erMRI response rate (64% versus 86%), while Trial 2 showed an opposite trend (78% versus 63%). None of these comparisons were statistically significant (P≥0.40). There was no clear relationship between achieving a PSA and erMRI response.

Biochemical Recurrence and Survival

The median follow-up post-radical prostatectomy for Trial 1 was 8.7 years (range, 0.1–11.9 years), for Trial 2 was 3.5 years (range, 0.8–5.3 years), and for the combined cohort was 4.2 years (range, 0.1–11.9 years). Among the 53 patients that underwent radical prostatectomy, 62% (33/53) developed a biochemical recurrence. The median time to biochemical recurrence from the date of surgery was 2.2 years (95% CI: 1.0–4.4 years). There were 5 deaths at time of the analysis (all 5 patients had developed biochemical recurrence). Four deaths were due to prostate cancer and 1 was from relapsed esophageal cancer. The median overall survival post-surgery has not been reached. The survival rate was 92% (95% CI: 77%–98%) at 5-years and 71% (36%–89%) at 10-years post-radical prostatectomy.

Association Between Response Measures and Biochemical Recurrence

The results of the univariable analysis correlating erMRI and PSA response with biochemical recurrence are shown in Table 3. There were trends observed for longer time to biochemical recurrence in patients achieving a PSA response and in patients not achieving an erMRI response. When patients were classified into 4 groups based on erMRI and PSA response, patients with erMRI response but lacking PSA response had the poorest outcome. However, these associations did not reach statistical significance. Of note, a higher proportion of patients with Gleason scores > 7 or T3 stage disease achieved an erMRI response, although these associations did not reach statistical significance (data not shown).

The association between erMRI response and time to biochemical recurrence was subsequently explored in multivariable models adjusted for baseline tumor characteristics. Two multivariable models were constructed as shown in Table 4. We did not detect a significant association between PSA response and the time to biochemical recurrence (HR=0.58, 95% CI 0.25–1.33, p=0.20). However, both models revealed that an erMRI response was paradoxically associated with a shorter time to biochemical recurrence.

Discussion

Intermediate endpoints could potentially speed the development of neoadjuvant therapeutic approaches for the treatment of high-risk clinically localized prostate cancer by providing a basis for screening the activity of novel regimens in the phase II setting and prioritizing regimens for definitive investigation. While intermediate endpoints need not necessarily fulfill the criteria of “surrogacy” [11] to prove useful, such measures should demonstrate an association with the ultimate health outcome of interest. In the current analysis, we explored two potential intermediate endpoints utilized in trials of neoadjuvant docetaxel. Post-treatment declines in PSA were not significantly associated with biochemical recurrence on univariable or multivariable analysis, though trends were observed which did not reach statistical significance possibly due to the small sample size. Paradoxically, erMRI response did not correlate with prolonged time to biochemical recurrence and, in fact, may be associated with worse outcomes.

The potential reason for the paradoxical association between erMRI response and biochemical recurrence is not entirely clear. One possible explanation may be related to a

higher likelihood of objective regressions in more highly proliferative and/or aggressive primary tumor lesions. Chemotherapy may be sufficient to shrink such tumors, though treatment is clearly insufficient to eradicate these tumors (as evidenced by the lack of complete pathologic responses) and may, likewise, be insufficient to eradicate micrometastatic disease. While this is purely speculative, a higher proportion of patients in the current analysis with Gleason > 7 disease achieved an erMRI response, though this association did not reach statistical significance. Post-treatment decrease in tumor volume on MRI has been associated with prolonged time to recurrence in other tumors, such as breast cancer. [14] However, these disparate results may be related to the increased likelihood of achieving “deeper” tumor regressions (e.g., complete pathologic responses) in breast cancer compared with prostate cancer.

There are several limitations to the current study. This is a retrospective analysis though the erMRI measurements and PSA’s were collected prospectively in the respective trials. The sample size is relatively small and involved pooling two trials with similar, though not identical, characteristics. However, to our knowledge, this is the first analysis exploring the correlation between erMRI and/or PSA changes after neoadjvant chemotherapy and long-term clinical outcomes in prostate cancer. The majority of patients in the current analysis received bevacizumab in combination with docetaxel and the degree to which this regimen, impacting the tumor neovasculature, may impact the measurement of tumor volume on MRI independently of actual tumor regressions is unclear. The current analysis correlated post-treatment changes in erMRI and PSA with biochemical recurrence, rather than overall survival, given the small number of deaths in the cohort. However, the vast majority of patients that die due to prostate cancer first experience biochemical recurrence, and biochemical recurrence is particularly ominous in this population of patients with poor baseline prognostic features. [15] Given these limitations, the findings of the current analysis should ultimately be validated in an independent cohort.

Another important limitation is the MRI technique itself. The MRI techniques employed in these studies are no longer state of the art. Since 2007 and 2009, two major changes have occurred in prostate MRI which were not available for these protocols. The use of 3T magnets, which allow higher signal to noise ratios, have lead to improvements in characterization of individual lesions within the gland. Perhaps more importantly is the lack of diffusion sequences (DWI). The DWI, and the accompanying attenuation diffusion coefficient (ADC) values, has had a major impact on MRI. The ADC values have been shown to not only improve focal lesion detection but have even shown correlations with Gleason grade. [16–19] Whether the availability of these technological advances would have altered the outcome of the current analysis can only be speculated upon, though future studies with next generation imaging techniques are warranted.

The results of this analysis may only apply to neoadjuvant trials exploring cytotoxic chemotherapy. Recently, the use of novel hormonal regimens in the neoadjuvant setting has yielded more impressive tumor regressions including a subset of patients achieving near, and even complete, pathologic responses. [20–21] These major pathologic responses may represent superior intermediate endpoints for neoadjuvant prostate cancer trials, but will also ultimately also need to be correlated with long-term clinical outcomes. The degree to which

erMRI changes may better correlate with long term outcomes in the context of these more active neoadjuvant regimens also warrants investigation.

The current analysis reveals that 1.5T erMRI response on T2 weighted images does not correlate with a longer time until biochemical recurrence in patients with high-risk localized prostate cancer treated with neoadjuant docetaxel-based therapy, and may be associated with inferior clinical outcomes. These findings do not support the use of erMRI response, utilizing the techniques employed in these studies, as a primary endpoint in future trials of neoadjuvant chemotherapy in prostate cancer. However, more active recently developed neoadjuvant hormonal therapy regimens may finally allow the exploration of major pathologic responses as intermediate endpoints in this clinical disease state, expediting the integration of multimodality approaches for high risk localized disease. In addition, prospective studies should continue to integrate next generation imaging technologies, as secondary outcome measures, in an effort to develop non-invasive intermediate endpoints.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: a cancer journal for clinicians. 2012; 62:10–29. [PubMed: 22237781]
2. Ganz PA, Barry JM, Burke W, et al. National Institutes of Health State-of-the-Science Conference: role of active surveillance in the management of men with localized prostate cancer. Annals of internal medicine. 2012; 156:591–595. [PubMed: 22351514]
3. Kibel AS, Ciezki JP, Klein EA, et al. Survival Among Men With Clinically Localized Prostate Cancer Treated With Radical Prostatectomy or Radiation Therapy in the Prostate Specific Antigen Era. J Urology. 2012; 187:1259–1265.
4. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. Jama. 1998; 280:969–974. [PubMed: 9749478]
5. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. Journal of the National Cancer Institute. 1998; 90:766–771. [PubMed: 9605647]
6. Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. Jama. 1997; 277:1445–1451. [PubMed: 9145716]
7. Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol. 2009; 27:4300–4305. [PubMed: 19636023]
8. Chi KN, Chin JL, Winquist E, Klotz L, Saad F, Gleave ME. Multicenter phase II study of combined neoadjuvant docetaxel and hormone therapy before radical prostatectomy for patients with high risk localized prostate cancer. The Journal of urology. 2008; 180:565–570. discussion 70. [PubMed: 18554663]
9. Dreicer R, Magi-Galluzzi C, Zhou M, et al. Phase II trial of neoadjuvant docetaxel before radical prostatectomy for locally advanced prostate cancer. Urology. 2004; 63:1138–1142. [PubMed: 15183967]
10. Febbo PG, Richie JP, George DJ, et al. Neoadjuvant docetaxel before radical prostatectomy in patients with high-risk localized prostate cancer. Clin Cancer Res. 2005; 11:5233–5240. [PubMed: 16033841]

11. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med. 1989; 8:431–440. [PubMed: 2727467]
12. Esserman LJ, Berry DA, Demichele A, et al. Pathologic Complete Response Predicts Recurrence-Free Survival More Effectively by Cancer Subset: Results From the I-SPY 1 TRIAL--CALGB 150007/150012, ACRIN 6657. J Clin Oncol. 2012; 30:3242–3249. [PubMed: 22649152]
13. Ross RW, Galsky MD, Febbo P, et al. Phase 2 study of neoadjuvant docetaxel plus bevacizumab in patients with high-risk localized prostate cancer : A Prostate Cancer Clinical Trials Consortium trial. Cancer. 2012; 118:4777–4784. [PubMed: 22282219]
14. Partridge SC, Gibbs JE, Lu Y, et al. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. AJR Am J Roentgenol. 2005; 184:1774–1781. [PubMed: 15908529]
15. Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU international. 2012; 109:32–39. [PubMed: 21777360]
16. Hoeks CM, Barentsz JO, Hambrock T, et al. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. Radiology. 2011; 261:46–66. [PubMed: 21931141]
17. Margel D, Yap SA, Lawrentschuk N, et al. Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: a prospective cohort study. The Journal of urology. 2012; 187:1247–1252. [PubMed: 22335871]
18. Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. The Journal of urology. 2011; 186:1818–1824. [PubMed: 21944089]
19. van As NJ, de Souza NM, Riches SF, et al. A study of diffusion-weighted magnetic resonance imaging in men with untreated localised prostate cancer on active surveillance. European urology. 2009; 56:981–987. [PubMed: 19095345]
20. Mostaghel EA, Nelson P, Lange PH, et al. Neoadjuvant androgen pathway suppression prior to prostatectomy. ASCO Meeting Abstracts. 2012; 30:4520.
21. Taplin M-E, Montgomery RB, Logothetis C, et al. Effect of neoadjuvant abiraterone acetate (AA) plus leuprolide acetate (LHRHa) on PSA, pathological complete response (pCR), and near pCR in localized high-risk prostate cancer (LHRPC): Results of a randomized phase II study. ASCO Meeting Abstracts. 2012; 30:4521.

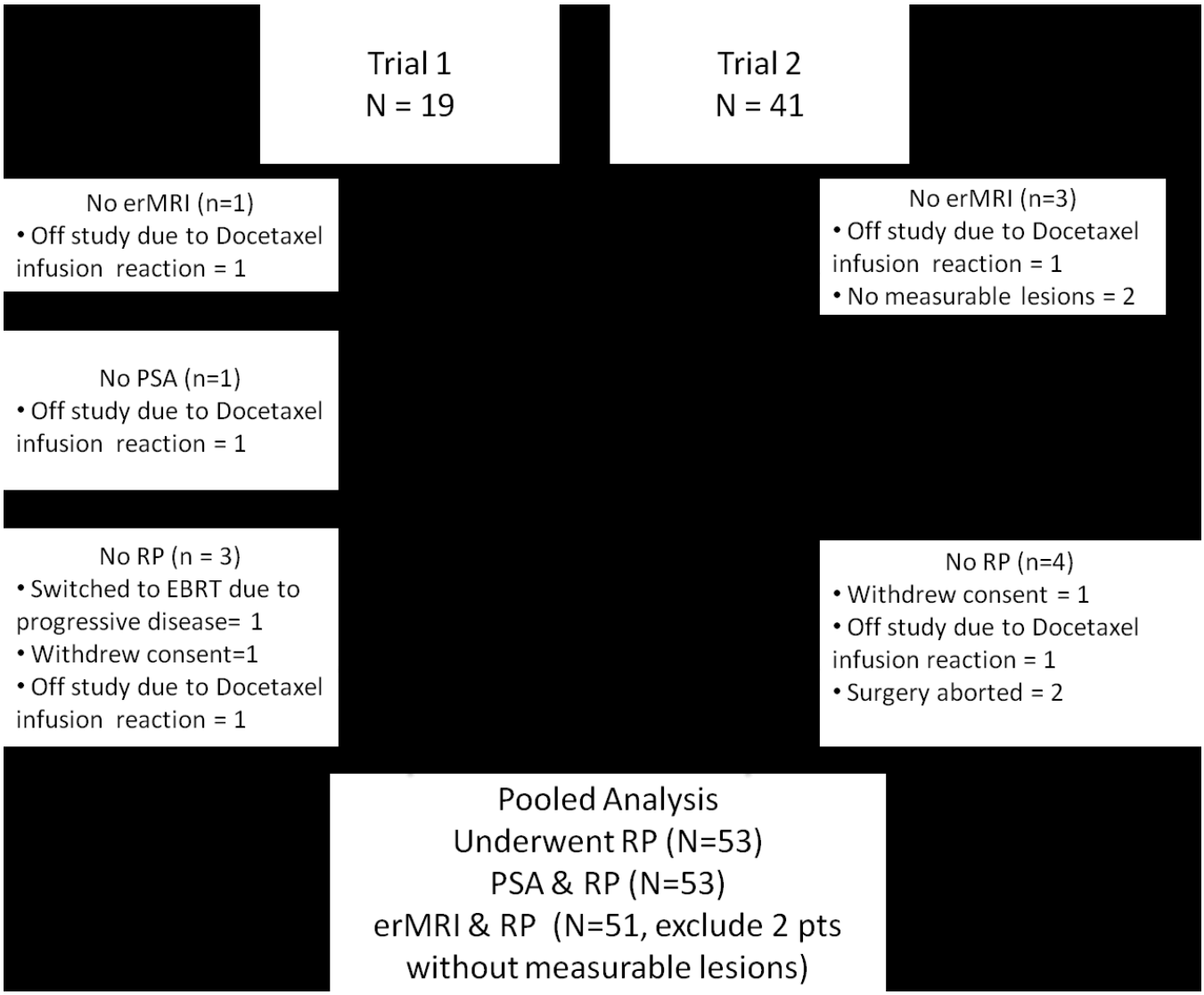

Figure 1.
Flowchart detailing study population included in the final analysis (erMRI, endorectal MRI; PSA, prostate specific antigen; RP, radical prostatectomy; pts, patients).

Table 1

Patient, treatment, and tumor characteristics

	Trial 1 (n=19)	Trial 2 (n=41)	All (n=60)
	N (%) or Median (range)	N (%) or Median (range)	N (%) or Median (range)
Age	54 (43–63)	55 (41–67)	55 (41–67)
Baseline PSA, ng/mL	15.6 (3.2–51.3)	10.1 (2.1–72.4)	10.7 (2.1–72.4)
Clinical T Stage			
cT1c	9 (47.4)	8 (19.5)	17 (28.3)
cT2	7 (36.8)	20 (48.8)	27 (45.0)
cT3	3 (15.8)	13 (31.7)	16 (26.7)
Clinical N Stage*			
cN0	19 (100)	12 (29.3)	31 (51.7)
cNX	-	29 (70.7)	29 (48.3)
Gleason Score (on biopsy)			
6	5 (26.3)	1 (2.4)	6 (10.0)
7	6 (31.6)	10 (24.4)	16 (26.7)
8	2 (10.5)	15 (36.6)	17 (28.3)
9	6 (31.6)	14 (34.1)	20 (33.3)
10	-	1 (2.4)	1 (1.7)
Neoadjuvant duration**	6.4 (5.4–7.9)	5.3 (2.7–6.0)	5.6 (2.7–7.9)
Pathologic T stage***			
pT2a	1 (6.3)	2 (5.4)	3 (5.7)
pT2b	5 (31.3)	-	5 (9.4)
pT2c	-	12 (32.4)	12 (22.6)
pT3a	2 (12.5)	10 (27.0)	12 (22.6)
pT3b	7 (43.8)	13 (35.1)	20 (37.7)
pT4	1 (6.3)	-	1 (1.9)
Pathologic N Stage***			
pN0	16 (100)	29 (78.4)	45 (85.1)
pN1	-	7 (18.9)	7 (13.2)
pNX	-	1 (2.7)	1 (1.9)
Extracapsular extension***			
No	6 (37.5)	14 (37.8)	20 (37.7)
Yes	10 (62.5)	23 (62.2)	33 (62.3)
Seminal vesicle involvement***			
No	8 (50.0)	24 (64.9)	32 (60.4)
Yes	8 (50.0)	13 (35.1)	21 (39.6)

*Baseline computed tomography scans were not mandated, but all patients underwent baseline endorectal magnetic resonance imaging and were excluded if pelvic lymph nodes measured >2 cm unless those lymph nodes were biopsy proven as benign.

**Time in months from initiation of chemotherapy to surgery.

***Excluding three patients in Trial 1 and four patients in Trial 2 who did not undergo radical prostatectomy

Table 2

erMRI and PSA Response to Neoadjuvant Chemotherapy

	PSA response	N*	Minor Response N (%)	Partial response N (%)	Minor + Partial Response N (%)	P
Trial 1	No	7	3 (43)	3 (43)	6 (86)	0.60
	Yes	11	6 (55)	1 (9)	7 (64)	
Trial 2	No	32	12 (38)	8 (25)	20 (63)	0.47
	Yes	9	3 (33)	4 (44)	7 (78)	
All	No	39	15 (39)	11 (28)	26 (67)	0.99
	Yes	20	9 (45)	5 (25)	14 (70)	

*Excluding 1 patient from Trial 1 whose erMRI and PSA response were both unevaluable; including three patients in Trial 2 were not evaluable for erMRI response but evaluable for PSA response. Reasons of unevaluable response are detailed in Figure 1.

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Table 3

Associations of time to biochemical recurrence with response to neoadjuvant chemotherapy

		Log-rank test			Cox regression		
	N	**2-year Relapse free (%) (95%CI)**	**p-value**	**Stratified p-value***	**Hazard ratio (95% CI)**	**P-value**	**Stratified p-value***
PSA response							
Yes	18	65 (39, 83)	0.16	0.51	0.59 (0.28,1.25)	0.17	0.51
No	35	42 (25, 58)			reference		
erMRI response							
PR	14	31 (10, 55)	0.08 (0.06**)	0.10 (0.06**)	3.00 (1.10,8.15)	0.10 (0.06**)	0.12 (0.07**)
MR	23	44 (23, 63)			1.99 (0.77, 5.16)		
Non-responder	14	71 (39, 88)			reference		
*Combination of PSA and erMRI response****							
PSA and erMRI response	12	56 (24, 79)	0.09	0.20	1.17 (0.38,3.61)	0.14	0.23
erMRI response only	25	31 (14, 50)			2.00 (0.74,5.42)		
PSA response only	5	80 (20, 97)			0.28 (0.03,2.44)		
Non-responder	9	65 (25, 87)			reference		

*Stratified by protocol

**If PR and MR were combined.

***erMRI response included both PR and MR.

erMRI, endorectal MRI; PR, partial response, MR, minor response

Table 4

Association of erMRI response with time to biochemical recurrence in multivariable models

Parameter	Comparison	HR	95% CI	p value
Model 1				
Gleason score	>7 vs. ≤7*	2.21	0.97, 5.05	0.06
Clinical T stage	T3 vs. T1-2*	2.45	1.12, 5.35	0.02
erMRI response				0.10
	MR vs. NR*	2.13	0.82,5.57	0.12
	PR vs. NR*	3.05	1.10,8.44	0.03
Model 2				
Gleason score	>7 vs. ≤7*	2.31	1.00, 5.36	0.05
Clinical T stage	T3 vs. T1-2*	2.04	0.90, 4.63	0.09
erMRI response	MR+PR vs. NR*	2.47	1.00,6.13	0.05
PSA response	Yes vs. No*	0.58	0.25,1.33	0.20

*reference group

erMRI, endorectal MRI; MR, minor response; PR, partial response; NR, no response