Stamp Test Delivers Message on Erectile Dysfunction After High-dose Intensity-modulated Radiotherapy for Prostate Cancer

Lanea M. M. Keller, Fox Chase Cancer Center
Mark K. Buuyounouski, Fox Chase Cancer Center
Dennis Sopka, Fox Chase Cancer Center
Karen Ruth, Fox Chase Cancer Center
Tracy Klayton, Fox Chase Cancer Center
Alan Pollack, University of Miami
Deborah W. Bruner, Emory University
Richard Greenberg, Fox Chase Cancer Center
Robert Price, Fox Chase Cancer Center
Eric M. Horwitz, Fox Chase Cancer Center

Journal Title: Urology
Volume: Volume 80, Number 2
Publisher: Elsevier: 12 months | 2012-08-01, Pages 337-342
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.urology.2012.04.048
Permanent URL: https://pid.emory.edu/ark:/25593/s9dzh

Final published version: http://dx.doi.org/10.1016/j.urology.2012.04.048

Copyright information:
© 2012 Elsevier Inc.
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed August 12, 2019 5:51 AM EDT
THE STAMP TEST DELIVERS THE MESSAGE ON ERECTILE DYSFUNCTION FOLLOWING HIGH DOSE IMRT FOR PROSTATE CANCER

Lanea M. M. Keller†, Mark K. Buuyounouski†, Dennis Sopka†, Karen Ruth‡, Tracy Klayton†, Alan PollackΦ, Deborah Watkins-BrunerΨ, Richard Greenberg‡, Robert Price†, and Eric M Horwitz†
†Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA
‡Biostatistics, Fox Chase Cancer Center, Philadelphia, PA
ΦRadiology Oncology Fox Chase Cancer Center, Philadelphia, PA
ΨSchool of Nursing, Emory University, Georgia, PA

Abstract

Objectives—To evaluate erectile function following high dose radiotherapy for prostate cancer using the international index of erectile function (IIEF), expanded prostate cancer index composite (EPIC), and stamp test.

Methods—Men with favorable and intermediate risk prostate cancer were assigned to receive prostate intensity modulated radiotherapy (IMRT) vs. an erectile tissue-sparing IMRT technique on a phase III randomized prospective study. The stamp test, IIEF, and EPIC questionnaires were completed at baseline, 6 months, one year, and two years after IMRT. Sexual Health Inventory for Men (SHIM) scores were abstracted from IIEF questionnaires. A partner questionnaire, designated IIEF-P, modeled after the IIEF but from the perspective of the partner, was collected.

Results—Ninety four men enrolled on the trial who completed at least one questionnaire or one stamp test were analyzed. The median age of the patient population was 62.5 years. The median RT dose was 76 Gy (range: 74–80 Gy). At 6-months and one year after high-dose IMRT, a positive stamp result significantly correlated with median EPIC sexual summary, sexual function (EF), and bother subscale scores. Additionally, 6-months after IMRT the stamp test correlated with median IIEF, IIEF EF domain, and SHIM scores. Robust concordance for the IIEF and SHIM results was appreciated between responding patients: partner pairs.

© 2012 Elsevier Inc. All rights reserved.

Corresponding Author: Eric M Horwitz, Professor and Chairman, Gerald E. Hanks, M.D. Chair in Radiation Oncology, Department of Radiation Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111, Phone: 215.728.2995, Fax: 215.728.2868, Eric.Horwitz@FCCC.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Abstract presented at the scientific session of the American Society of Radiation Oncology annual meeting 2010, 31st October – 4th November, 2010 at San Diego, CA, USA.
Conclusions—Nocturnal tumescence indicated by a positive stamp test correlates well with established quality of life questionnaires after IMRT. The stamp test should strongly be considered as an objective measure of erectile function in future studies of ED in prostate cancer patients.

Keywords
prostate cancer; intensity modulated radiotherapy; erectile dysfunction

Introduction

Potency preservation is a quality of life (QOL) outcome that, for many prostate cancer patients, may influence their selection of a treatment modality as much as the treatment's overall efficacy. While erectile dysfunction (ED) is a multi-faceted problem, it has been reported to occur in approximately one-quarter to one-half of men following treatment with external beam radiotherapy. The mechanism for ED, defined as "the inability to attain and maintain penile erection sufficient for satisfactory sexual performance" has been extensively studied. The physiology of erectile function depends on measurable findings such as innervation and blood flow, but also on more elusive influences such as psychosocial and psychosexual factors. The etiology of ED that arises after treatment for prostate cancer also depends on a number of patient specific factors, including age, medical comorbidities, self-image, pre-treatment sexual function, and choice of treatment modality. Post-operative ED is often caused by neurologic injury or compromise, while post-radiation ED may be related to vascular impairment and corporal fibrosis.

Means of assessing erectile function have included both subjective questionnaires and objective measurements. Historically, this was studied using physician reported outcomes and rates of resultant ED were less reliable than patient-reported outcomes. The International Index of Erectile Function Questionnaire (IIEF) is a validated 15-item questionnaire organized into five domains including: erectile function, orgasmic function (OF), sexual desire (SD), intercourse satisfaction (IS), and overall sexual satisfaction (OSS). The IIEF has high internal consistency and discriminate validity as demonstrated by the scales' ability to differentiate between patients with ED and age-matched controls. The IIEF positively correlates with clinical interviews of sexual function. Indeed IIEF question 3 (Q3; ability to achieve penetration) and question 4 (Q4; ability to maintain penetration) were used as primary endpoints in the first two large-scale clinical trials of sildenafil in the USA. Additionally, the Sexual Health Inventory for Men (SHIM), consisting of questions 2, 4, 5, 7, and 15 from the IIEF, has been validated as a brief diagnostic tool and is widely used as an ED screening measure in clinical practice. A variation on the IIEF questionnaire, the IIEF-P, was developed at Fox Chase Cancer Center (FCCC) for the current study, as a companion to the patient version. The IIEF-P was specifically designed to measure erectile dysfunction of the patient as perceived by the partner. The first set of questions (1–16) is identical to the IIEF taken by the patient. The second set of questions (17–20) is related to how the partner feels their sexual relationship with the patient has changed since his cancer diagnosis and therapy. The Expanded Prostate Index Composite is a robust 50-item quality of life questionnaire that addresses a broad spectrum of urinary, sexual, bowel, and hormonal symptoms in the setting of contemporary prostate cancer therapies. This instrument has been validated with test-retest reliability, high internal consistency, and shows correlation between function and bother subscales.

Multiple objective diagnostic tests for physiologic erectile capability exist, including somatosensory evoked potentials, bulbocavernous reflex latency, penile electromyography, color duplex Doppler ultrasound, dynamic infusion cavernosometry, and pharmaco testing. Use of these measures on a large scale would be needed for a clinical trial, while

*Urology. Author manuscript; available in PMC 2013 August 01.*
providing important data, would also be expensive and inconvenient for the patient and potentially inhibit trial participation. The postage stamp test is a cost-effective and non-invasive objective evaluation of erectile function based on physiologic nocturnal tumescence. This test entails securing a row of self-adhesive stamps around the base of the penis (Figure 1) at bedtime. A nocturnal erection causes the circle of stamps to tear and is indicative of erectile function and would be considered a positive result.

In 2003, a phase III prospective randomized trial between standard high dose intensity modulated radiation therapy (IMRT) and erectile tissue sparing IMRT was initiated for prostate cancer patients treated at FCCC in an effort to define the rate of ED following treatment and to test the clinical significance of erectile tissue dose sparing. Erectile function was assessed subjectively through the use of questionnaires and objectively with the stamp test. Using the collected ED data, we have studied the correlation between the objective postage stamp test and QOL questionnaires prior to and at defined intervals following high dose IMRT. The stamp test has not previously been studied in the evaluation of ED after radiation for prostate cancer.

**METHODS AND MATERIALS**

Men with favorable to intermediate risk prostate cancer were enrolled and treated on an IRB approved randomized blinded clinical trial investigating outcomes following intensity modulated radiation therapy (IMRT) with and without erectile tissue dose sparing at FCCC; informed consent was obtained prior to enrollment on the study. The cohort for the current study consists of all men treated on this trial who completed at least one questionnaire or stamp test at the time of analysis. Analysis between the randomization arms could not be performed as this trial continues to accrue.

Low-risk prostate cancer patients were defined as having a clinically palpable T1a–T2a, PSA < 10 ng/ml, and Gleason Score (GS) ≤ 6 with ≤ 3 positive biopsy cores. Patients with intermediate risk prostate cancer had a clinical palpation stage T1a-T2c, PSA 10–20, GS ≤ 6 with greater than 3 biopsy cores positive or GS 7. Additional eligibility criteria included adequate pre-treatment erectile function defined as a combined score ≥ 6 for question #3 (Q3; ability to achieve penetration) and question 4 (Q4; ability to maintain penetration) on the IIEF. Exclusion criteria included patients with previous pelvic radiotherapy, radical prostatectomy, penile prosthesis, or current use of intraurethral suppositories or injection ED therapy. No patient received androgen deprivation therapy.

The erectile tissue sparing IMRT technique used has been previously reported. Briefly, patients were immobilized in an alpha cradle (Smithers Medical Products, Akron, OH) cast and underwent a CT simulation (Philips PQ5000; Philips, Cleveland, OH) followed by MRI simulation (Philips Proview; Philips Medical Systems, Cleveland, OH). The target and avoidance structures were defined on fused CT/MRI simulation. The clinical target volume (CTV) was defined as the prostate and proximal seminal vesicles (caudal 9 mm) for low risk patients and the prostate, proximal, and distal seminal vesicles for intermediate risk patients. The CTV was expanded by 8 mm except posteriorly where it was expanded 5–6 mm, to produce the planning target volume (PTV).

As evidence supporting dose escalation emerged, the radiation prescription dose was increased from 74 and 78 Gy for low-and intermediate-risk patients to 78 and 80 Gy, respectively. IMRT plans were evaluated by dose-volume histogram analysis. The PTV was required to receive ≥ 95% of the prescription dose with < 20% heterogeneity. Our institutional normal tissue dose constraints are as follows: rectal volume (rectum and entire contents from sigmoid flexure to bottom of ischial tuberosities) receiving > 65 Gy and > 40

*Urology. Author manuscript; available in PMC 2013 August 01.*
Gy were limited to ≤ 17% and ≤ 35%, respectively; bladder volume (bladder and contents) receiving > 65 Gy and > 40 Gy were limited to ≤ 25% and ≤ 50%, respectively; and < 10% of the femoral heads were to receive > 50 Gy. For those randomized to erectile tissue sparing IMRT, 90% of the penile bulb was limited to ≤ 15 Gy and 90% of the corporal bodies was limited to ≤ 7 Gy. Daily prostate localization was performed using transabdominal B-mode acquisition and targeting (BAT) ultrasound (NOMOS Cranberry Township, PA), gold seed fiducial markers with kV orthogonal imaging, daily cone beam CT, or Calypso (Calypso Medical Technologies, Inc. Seattle, WA) radiofrequency localization.

QOL measurements including the IIEF, IIEF-P, and EPIC questionnaires were completed pre-treatment and at 6, 12, and 24 months. The IIEF-P results were collected on the same schedule as the patient’s results and were to be completed independently by the responding partner, to minimize potential bias from the patient.

The patient was instructed to complete the stamp test over three consecutive nights pretreatment, 6, 12, and 24 months after radiation therapy. The test was considered positive if the patient reported at least one incidence of a broken stamp. Scores for the EF domain (questions 1, 2, 3, 4, 5, 15) of the IIEF were determined, as well as EPIC sexual summary (questions 17–25), sexual function (questions 56 – 64), and bother (questions 65–68) subscores. SHIM scores were derived from the IIEF.

For those with stamp results and questionnaire responses, differences in scores by the corresponding stamp test results were determined using the Wilcoxon rank sum test. Responses to IIEF questions 3 and 4 were compared to the corresponding stamp test results using Fisher’s exact test. For patients and partners who completed IIEF questionnaires, concordance between results were measured by Spearman rank correlation with 95% confidence limits derived using Fisher’s z transformation. Data were analyzed using SAS/STAT software (versions 9.12). The collection, storage, and retrieval of data were all done in compliance with the hospital’s Institutional Review Board and the Health Insurance Privacy and Portability Act.

RESULTS

Patient characteristics are detailed in Table 1. Of 113 men entered onto the study, 94 men completed at least one questionnaire or one stamp test at the time of analysis. The median age of this population was 62.5 years, most patients were Caucasian (81.9%) with a median BMI of 28 (21.2–40.6). The majority of patients had clinical T1c (76.6%) disease of Gleason 6 (3 + 3) scoring (88.3%). The median pretreatment PSA was 6.2 ng/ml. Prior to IMRT 10 patients (9%) reported taking a phosphodiesterase type 5 inhibitor and no patient received androgen deprivation therapy. Most patients received ≥ 76 Gy; the median RT dose was 76 Gy (range: 74–80 Gy).

Overall compliance with the stamp test was low and decreased over time: there were 68 stamp test responders at baseline, 33 at 6 months, 32 at one year, and 30 at two years. Questionnaire response rates were higher with 88 at baseline, 43 at 6 months, 40 at one year, and 36 at two years. Both an IIEF and a stamp test were completed by 66 at baseline, 33 at 6 months, 31 at one year, and 29 patients at two years. When comparing responders to non-responders, with respect to QOL questionnaire results, responders at baseline (p = 0.02) and those submitting one or more follow-up questionnaires (p = 0.04) after IMRT were more likely Caucasian. Otherwise responders and nonresponders at baseline well matched with respect to age, Gleason score, T stage, BMI, reported use of phosphodiesterase type 5 inhibitors, and smoking history. Responders with one or more follow-up questionnaires and
a reported stamp test tended to be older with a median age of 62.5 years (range 52–73) as compared the median age of 59 years (range 42–75) for non-responders (p = 0.002).

After IMRT a positive stamp result was associated with higher median EF domain score as compared to those with a negative stamp result (Figure 2). At six months after IMRT, median EF domain scores (score: 24 vs. 11, p = 0.05) and SHIM scores (score: 20 vs. 10, p = 0.04) were significantly higher in those reporting a positive stamp test. Median overall IIEF scores were significantly higher at one year after IMRT for patients with a positive vs. negative stamp test (score: 64 vs. 35, p = 0.03). Due to the small number of response categories, IIEF questions 3 and 4 were analyzed as binary groups (where responses of “Almost never/never”, “A few times”, or “Sometimes” was considered as the presence of ED (ED+) and “Most times” and “Almost always/always” was considered a lack of ED (ED −)). Based on IIEF question 4, 86% of ED-respondents reported a positive stamp test as compared to 44% of ED+ respondents one year after IMRT (p=0.03). At two years after IMRT, 90% of ED− respondents had a positive stamp result vs. 43% of ED+ respondents for question #3 (p=0.02), and 89% of ED− had a positive stamp result vs. 50% of ED+ patients for question 4, (p=0.04). When analyzing patient: partner pairs, robust and significant correlation between patient’s and their partner’s IIEF scores and EF domain scores was observed; similar correlation was observed with patient and partner SHIM scores after IMRT, as detailed in Table 2.

At six months and one year after high dose IMRT, patients with a positive stamp test had significantly higher median EPIC sexual summary scores (71 vs. 48 at 6 months, p = 0.007; 77 vs 52 at 1 year, p = 0.03), sexual function (71 vs.. 47 at 6 months, p = 0.008; 71 vs. 47 at 1 year, p =0.01) and sexual bother (81 vs. 38 at 6 months, p=0.005; 87 vs. 47 at 1 year, p = 0.05) subscale scores, as compared to those reporting a negative stamp result.

**DISCUSSION**

With modern treatment modalities we can achieve excellent cancer control of early and intermediate risk prostate cancer such that the associated impact on a patient’s quality of life has increasingly become the driving force behind the development of more sophisticated techniques. Most reports have historically focused on overall outcomes and associated bowel and bladder toxicities after radiation therapy. Perhaps not surprisingly, studies have shown concordance between physician and patient reported ED outcomes. In a study of erectile dysfunction after brachytherapy, MacDonald et al.\(^\text{21}\) reported a comparison of physician and patient reported ED rates for 342 patients who were potent prior to brachytherapy implant. Physicians documented ED rates of 57% and 48% at one and two years, respectively. When patient reported rates were examined, they found significantly higher rates of reported ED: 70% at one year and 66% at two years after brachytherapy.

Historically self-administered questionnaires evaluating erectile function were commonly employed and tended to be highly variable and largely unvalidated. However with the validation and acceptance of the IIEF in 1997 and EPIC in 2000, the possibility of comparisons between studies for patient-reported ED became a reality. It has become increasingly clear that ED is more than simply a physiologic issue but can be affected by other factors, including libido and general satisfaction with one’s sexual life. Both the IIEF and EPIC questionnaires attempt to address these multiple contributing elements. Objective measure of spontaneous erections provides knowledge regarding the potential etiology of ED (i.e. organic versus psychological) and may serve to compliment the findings obtained through subjective questionnaires. While several objective tests such as somatosensory evoked potentials, bulbocavernous reflex latency, penile electromyography, color duplex Doppler ultrasound, dynamic infusion cavernosometry, and penile blood flow studies are
available these interrogations are awkward and invasive for the patient and are time consuming and expensive to the healthcare system.

One of the first investigations attempting to correlate objective and subjective assessments of ED comes from a 1984 report from Goldstein et al, in which 23 patients underwent objective assessment of erectile functioning in addition to an interview by a psychologist after external beam radiation therapy. Following prostate radiation 12 subjects were noted to have altered function on objective examination and associated feelings of anxiety, depression, anger, fear of failure, and loss of masculinity were reported. In a 1999 study by Blander et al., 89 patients treated at an ED clinic underwent evaluation with questions from the IIEF and objective interrogation with penile blood flow studies (PBFS) consisting of pharmacologic testing and duplex Doppler ultrasound. Mean IIEF scores and Q3+4 values differed significantly for patients with normal PBFS as compared to patients with abnormal PBFS but IIEF scores were unable to statistically differentiate among the specific etiologies of ED for those with abnormal PBFS. An interesting finding was noted in that patients with normal penile blood flow studies had surprisingly low self-ratings of erectile performance. It was concluded for the specialist sexual inventory scores will not distinguish among the etiologies of ED and do not predict the results of objective testing. Recently Tokalti et al. investigated objective nocturnal penile tumescence and rigidity (NPTR) testing and corresponding IIEF- EF domain scores in patients evaluated through an ED clinic. Objective NPTR assessment revealed 67 of 90 (75%) men were potent despite 78 of 90 (87%) men reporting an IIEF-EF domain scores corresponding with ED (mild, moderate, or severe). Upon reevaluation of the IIEF sexual function disorders such as like libido loss, ejaculate- orgasmic disorders, and inadequate intercourse satisfaction were identified. For those patients in whom IIEF-EF domain scores were normal, so was objective assessment with NPTR.

In this study erectile function was evaluated both subjectively and objectively prior to and at specified intervals after high dose IMRT. A positive stamp test at six months to one year after IMRT was correlated with higher median EPIC sexual summary, bother, and function subscores. At six months after IMRT, a positive stamp test correlated with median overall IIEF, IIEF EF domain, and IIEF question #3 scores. Importantly, partner survey results demonstrated robust concordance with patient responses after high dose IMRT. Overall subjects reporting normal erectile function via questionnaire often reported a positive objective stamp result. However, similar to the results of the study by Tokalti et al., in those reporting some degree of ED via questionnaire, a negative stamp test was not necessarily observed suggesting that the mechanism of ED in these cases may not be physiologic but may be due to an underlying sexual function disorder. Importantly overall comparison of the objective (stamp test) results with those of the subjective (questionnaires) revealed that the stamp test correlates well with both the patient’s and partner’s perceived erectile function.

As evidenced by the decreasing number of respondents for both the surveys and stamp test over time, this study highlights the inherent difficulty of conducting quality of life studies due to non-compliance. However, the small population of this study should not diminish the strength of the significant correlations observed between a positive stamp test and subjective evaluation and the concordance observed between patient and partner responses. While further study into the mechanism(s) and prevention of radiation-induced impotence is required, both the standardized validated questionnaires, partner questionnaire, and the simple objective stamp test offer means to assess and track response to these interventions.
Acknowledgments

The authors thank Nick Zaorsky MD for his illustration of the stamp test.

References


Figure 1.
Graphic representation of the stamp test: a strip of stamps is secured around the base of the penis prior to sleep. A broken stamp upon waking signifies a positive test.
Figure 2.
Median patient reported EF domain scores over time after high dose IMRT.
Table 1

Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>N=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>median 62.5 (42–77)</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>median 6.2 (0.76–22.1)</td>
</tr>
<tr>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Gleason Score</td>
<td></td>
</tr>
<tr>
<td>G6</td>
<td>88.3% (83)</td>
</tr>
<tr>
<td>G7</td>
<td>11.7% (11)</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>76.6% (72)</td>
</tr>
<tr>
<td>T2a</td>
<td>20.2% (19)</td>
</tr>
<tr>
<td>T2b</td>
<td>3.2% (3)</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>74 Gy</td>
<td>19.1% (18)</td>
</tr>
<tr>
<td>76 Gy</td>
<td>64.9% (61)</td>
</tr>
<tr>
<td>78–80 Gy</td>
<td>16.0% (15)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>81.9% (77)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>18.1% (17)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>5.3% (5)</td>
</tr>
<tr>
<td>Former</td>
<td>57.5% (54)</td>
</tr>
<tr>
<td>Never</td>
<td>37.2% (35)</td>
</tr>
<tr>
<td>BMI (n=87)</td>
<td>median 28.0 (21.2–40.6)</td>
</tr>
</tbody>
</table>

Abbreviations: Body Mass Index (BMI)
Table 2

Patient: partner pair concordance on IIEF, Domain EF and SHIM scores.

<table>
<thead>
<tr>
<th>Time</th>
<th>N pairs</th>
<th>Rank Correlation</th>
<th>95% CI</th>
<th>p-value</th>
<th>N pairs</th>
<th>Rank Correlation</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49</td>
<td>0.82</td>
<td>0.70–0.89</td>
<td>&lt;0.0001</td>
<td>34</td>
<td>0.77</td>
<td>0.58–0.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>0.87</td>
<td>0.73–0.93</td>
<td>&lt;0.0001</td>
<td>20</td>
<td>0.82</td>
<td>0.59–0.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>0.84</td>
<td>0.69–0.93</td>
<td>&lt;0.0001</td>
<td>19</td>
<td>0.69</td>
<td>0.34–0.87</td>
<td>0.0011</td>
</tr>
<tr>
<td>24</td>
<td>27</td>
<td>0.94</td>
<td>0.87–0.97</td>
<td>&lt;0.0001</td>
<td>19</td>
<td>0.87</td>
<td>0.68–0.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF domain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49</td>
<td>0.68</td>
<td>0.49–0.81</td>
<td>&lt;0.0001</td>
<td>34</td>
<td>0.58</td>
<td>0.30–0.77</td>
<td>0.0003</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>0.86</td>
<td>0.72–0.93</td>
<td>&lt;0.0001</td>
<td>20</td>
<td>0.77</td>
<td>0.50–0.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>0.84</td>
<td>0.68–0.92</td>
<td>&lt;0.0001</td>
<td>19</td>
<td>0.73</td>
<td>0.41–0.89</td>
<td>0.0004</td>
</tr>
<tr>
<td>24</td>
<td>27</td>
<td>0.89</td>
<td>0.78–0.95</td>
<td>&lt;0.0001</td>
<td>19</td>
<td>0.76</td>
<td>0.46–0.90</td>
<td>0.0002</td>
</tr>
<tr>
<td>SHIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53</td>
<td>0.67</td>
<td>0.49–0.80</td>
<td>&lt;0.0001</td>
<td>37</td>
<td>0.54</td>
<td>0.26–0.73</td>
<td>0.0006</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>0.86</td>
<td>0.74–0.93</td>
<td>&lt;0.0001</td>
<td>20</td>
<td>0.78</td>
<td>0.52–0.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>0.85</td>
<td>0.71–0.93</td>
<td>&lt;0.0001</td>
<td>20</td>
<td>0.69</td>
<td>0.36–0.87</td>
<td>0.0007</td>
</tr>
<tr>
<td>24</td>
<td>29</td>
<td>0.86</td>
<td>0.72–0.93</td>
<td>&lt;0.0001</td>
<td>19</td>
<td>0.72</td>
<td>0.39–0.88</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

* The statistical analysis for patient: partner pair responses as a function of a negative stamp result were unable to be accurately calculated due to a limited cohort size.