Trends in Door-to-Thrombolysis Time in the Safe Implementation of Stroke Thrombolysis Registry

Effect of Center Volume and Duration of Registry Membership

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Background and Purpose—Shorter delays between symptom onset and treatment translate into better outcomes after ischemic stroke thrombolysis. There are considerable intercenter variations in treatment delivery. We analyzed the trends of door-to-needle times (DNTs) in the Safe Implementation of Thrombolysis in Stroke registry between 2003 and 2011.

Methods—We extracted from the Safe Implementation of Thrombolysis in Stroke registry (n=45 079) year of treatment, center code, DNT, sex, age, National Institutes of Health Stroke Scale, and comorbidity. For each center, the year they joined the registry and the annual volume of patients were determined (<5, 5–24, 25–49, 50–74, 75–99, and ≥100 patients/y).

Results—DNT was not available for 720 (1.6%) patients. The overall mean (SD) DNT was 73 (37) minutes with a median (interquartile range) of 67 (47–91) minutes. The DNT was 65 (46–90), 68 (50–92), and 72 (51–98) minutes for centers joined early (2003–2005), later (2006–2009), and recently (2009–2011), respectively. Center volume had more robust effect on DNT than year of treatment, and the shortest DNTs were seen in centers with volumes ≥100 patients/y. Earlier enrollment period was also associated with shorter delays.

Conclusions—Centers that joined the registry earlier and those with high annual volume achieved shorter DNT than centers that joined later and low-volume centers. However, in most of the centers, DNT did not change much during the registry period. A multicenter project aiming to reduce DNT is warranted. **(*Stroke*. 2015;46:1275-1280. DOI: 10.1161/STROKEAHA.114.007170.)**

Key Words: stroke ■ thrombolysis ■ thrombolytic therapy ■ time-to-treatment

See related article, p 1158.

It is widely recognized that the earlier thrombolysis is administered after stroke onset, the better the outcome.[1–5] In stroke thrombolysis, onset to treatment time can be divided into onset-to-door and door-to-needle time (DNT). The latter can be influenced by streamlining of all parts of the in-hospital thrombolysis process and improves with center experience. Patients with longer DNTs have a lower chance of achieving an excellent outcome (a modified Rankin Scale score of 0 or 1) at 3 months.[6]

We first studied overall temporal changes in DNT in centers registering patients into the Safe Implementation of Thrombolysis in Stroke (SITS)-International Stroke Thrombolysis registry (ISTR),[7] and we hypothesized that DNT is influenced by the center experience judged by the annual number of patients treated.

Patients and Methods

Study Setting

At the time of the data extraction, the SITS-ISTR was a collaboration of >750 clinical centers in >40 countries (45 079 patients). It includes data of unselected ischemic stroke patients treated with intravenous thrombolysis according to institutional guidelines. Its first part includes patients who were registered in the SITS monitoring study, which was required by the European Medicines Agency after granting of conditional license for alteplase in 2002. Details of the methods, management, and demographics of SITS can be found elsewhere.[7,8]

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Ethical approvals for this study were obtained in countries in which they were required; other countries approved the register for conduct as an anonymized audit.

Year of treatment, DNT, and center codes were electronically extracted from the SITS database. We also extracted sex, age, baseline National Institutes of Health Stroke Scale (NIHSS), and history of diabetes mellitus, hypertension, atrial fibrillation, and previous stroke. We then identified the year when centers started registering patients into the SITS registry and looked in detail at those which started in the first 3 years, ie, between 2003 and 2005, in the middle (2006–2008), and in the last 3 years, ie, between 2009 and 2011. As an additional analysis, we analyzed effect of early registration of centers, for example, within the first year (January 1, 2003 to December 31, 2003).

On the basis of the retrieved number of patients treated in the centers per year, we created 6 volume/y categories: <5, 5 to 24, 25 to 49, 50 to 74, 75 to 99, and ≥100 treated patients/y. A center was attributed to a volume/y category if it was in the category range at least for 3 subsequent years. We could not analyze the effect of the type of stroke center because primary, secondary, and tertiary stroke centers were not defined in 2002. Hence, each center was judged by how soon it started entering data into the SITS registry and by the number of patients treated annually. The center experience, however, was evaluated by the annual volume of patients and not by the length of SITS membership. The latter does not necessarily reflect the experience because some dedicated stroke centers might have joined the SITS later. Nonetheless, there is one exception. The centers that joined the SITS registry during 2003 can be considered as the most experienced because the European Authorities granted conditional license for stroke thrombolysis with alteplase in 2002. One of the license conditions was that all patients treated with thrombolysis must be registered into the SITS registry; hence, the centers that joined during 2003 (no center joined in 2002) were the centers with experience gained, for example, from the randomized controlled trials. The centers that joined the SITS registry after 2003 implemented the thrombolysis protocol later.

Statistical Analyses

DNT had a non-normal distribution. Temporal changes in DNT among the subsequent years of registration adjusted for the effect of center volume were studied with a model of generalized estimating equations (scale response and γ with log-link model). The model included the following covariates and factors: age, baseline NIHSS, sex, and medical history. About the medical history, the percentages of the missing data were between 1.5% and 2% except for dyslipidemia (10%), which was excluded from the model. The center code was included as a within-subject effect (random) in the generalized estimating equations model; the option for correlation matrix in SPSS was exchangeable. We also included the interaction between center volume and year of treatment in the model. In the simple model, we only tested year of treatment, center volume, NIHSS, and age. Because age was not statistically significant (P=0.76), it was not included in more complex models with comorbidities. Statistical significance was set at 0.05 (2-tailed). Analyses were performed on IBM SPSS 22 (IBM Corp, Armonk, NY).

Results

Between December 2002 and December 2011, 45 079 patients were included in the SITS-ISTR. DNT was not registered for 1.6% (720/45 079) of the patients. These were excluded from the analyses, and the final cohort size was 44 359 patients. Their median DNT was 67 (interquartile range, 47–91) minutes with a mean of 73 (SD, 37) minutes. The overall picture of DNT changes in the whole cohort and by volume category is shown in Figure 1A and 1B. Basic characteristics of the centers that joined the registry in one of the 3 periods (enrollment periods: 2003–2005, 2006–2008, and 2009–2011) are shown in Table 1.

The results of the generalized estimating equations model are outlined in Table 2. After adjustment for sex, NIHSS, and comorbidity, we saw a robust effect on DNT caused by center volume and the enrollment period but a less robust effect of the treatment year (note the differences in both Wald χ^2 and magnitude of β coefficients). The effect estimates are derived using a log-link function. For example, if we look at the effect of treatment year, every single minute of DNT in 2011 equals to 1.07 [exp(0.064)] minutes of DNT in 2003. So, a patient with DNT of 70 minutes in 2011 would have had DNT of 74.6 minutes in 2003. As another example from Table 3, every minute of DNT in small centers (<5 patients/y) equals to 0.67 [exp(-0.401)] minutes in large centers (≥100 patients/y). In line, a patient with DNT of 70 minutes in small centers would have had DNT of 47 minutes in large centers. Note that effect estimates of each individual variable are adjusted for all the other variables in the model. When adding the interaction between year of treatment and center volume into the model, we observed a significant interaction (P<0.001). However, the interaction was highly driven by large centers that joined the registry between 2003 and 2005. Results including the interaction are shown in Tables I and II in the online-only Data Supplement.

Because of the low number of cases in some of the volume categories (Table 1), we tested for the sensitivity of our main model (without interaction). For this purpose, we recoded the volume category, so that the largest category was set to >50 patients/y. The results were in line with the original model

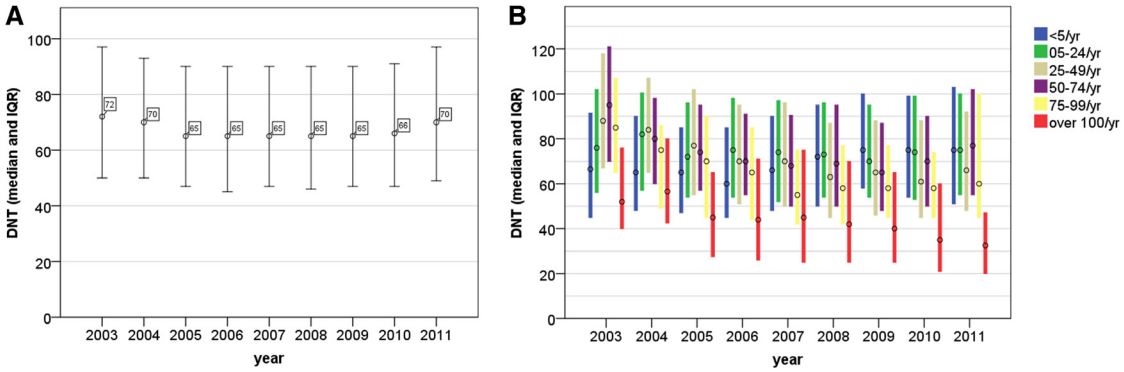

Figure 1. Temporal changes in door-to-needle time (DNT and interquartile range) in all centers at the patient level (**A**) and the center level (**B**).

Table 1. Basic Characteristics Based on Period of Joining the Registry

	Centers Joined in 2003–2005	Centers Joined in 2006–2008	Centers Joined in 2009–2011
DNT, min	65 (46–90)	68 (50–92)	72 (51–98)
Age, y	70 (61–77)	69 (59–76)	70 (60–77)
Women, %	43	42	44
Baseline NIH Stroke Scale	12 (7–17)	12 (7–17)	12 (7–17)
Diabetes mellitus, %	17.4	16.3	18.4
Hypertension, %	64.0	62.4	65.5
Atrial fibrillation, %	25.5	23.7	25.5
Previous stroke, %	13.3	13.0	12.2
No. of countries	28	29	26
No. of centers	379	243	131
Total no. of patients	32 182	9356	2821
No. of centers/patients per volume category			
<5 patients/y	239/8030	147/1831	110/1341
5–24 patients/y	88/7625	83/4639	19/951
25–49 patients/y	32/6619	11/2091	0
50–74 patients/y	11/3820	1/379	1/203
75–99 patients/y	5/2542	1/416	0
≥100 patients/y	4/3546	0	1/326

If not otherwise stated, the data are presented as median (interquartile range). DNT indicates door-to-needle time; and NIH, National Institutes of Health.

with the only exception that DNT in 2003 was not significantly different from 2011 (data not shown).

The temporal changes of DNT in patients from the centers that started within 2003 (21 countries, 137 centers, and 15 197 patients) are shown in Figure 2. Their median DNT shortened from 72 to 59 minutes between 2003 and 2011. The overall median DNT of these centers was 62 (42–89) minutes when compared with 70 (50–93) minutes in the centers that joined after 2003. When we performed the generalized estimating equations model only with the centers that joined the registry during 2003, we observed similar effect of center volume; however, the effect of year of treatment had a different profile (β coefficients and Wald χ^2 in Table 3). Specifically, in these centers, DNT continuously declined until 2008 but then did not significantly change after 2008. For the comparison with the whole cohort (Table 2), DNT was the same in 2011 (the reference year) as it was in 2003 and 2004, with only mildly lower DNTs in years 2005 to 2010. Thus, those centers that joined the registry already in 2003 have reduced DNT over time, as evidenced by the 2003-only analysis (Table 3), but by including all centers, the change over time is attenuated.

Discussion

Thrombolysis is a complex intervention, which required reorganization of services and specific staff training when it was first introduced. Achievement of fast DNTs is only possible with efficient and well-rehearsed internal processes. It is therefore expected that DTN improves with time as centers gain more experience. However, this study shows that DNT did not change much overall during the first decade of the SITS registry (2002–2011; Figure 1A). This is in line with the data from Get With The Guidelines program.[9] The observed annual changes in DNT can be better explained by center volume than the year of treatment (Table 2). The most robust annual DNT changes were observed in centers that joined the SITS within the first year (2003; Figure 2; Table 3). Temporal DNT profile in these centers was different from the whole cohort (Tables 2 and 3), which suggests that their streamlining of the factors known to be associated with DNT was on a high level. In contrary, in centers that joined the SITS relatively late (after 2009), there were no annual differences in DNT whatsoever. This might suggest that some of the learning from the early adopters was transferred to later registering centers and that the process rather than individual experience is a major factor.

Our observation of patient volume being the strongest determinant of DNT was reported also elsewhere.[9] The effect of volume held true even in centers that joined the SITS registry after 2009. The most robust annual decrease in DNT was observed in centers with high volume of patients (≥100/y and 75–99/y; Tables 2 and 3) even when adjusting for the interaction between center volume and year of treatment (arising

Table 2. Generalized Estimating Equations Model for the Whole Cohort

Parameter	β	SE	Wald χ^2	*P* Value
Year				
2003	0.064	0.018	12.0	<0.01
2004	0.027	0.014	3.5	0.06
2005	−0.035	0.012	7.9	<0.01
2006	−0.044	0.012	13.5	<0.001
2007	−0.025	0.012	4.7	<0.05
2008	−0.038	0.011	11.5	<0.01
2009	−0.043	0.011	16.6	<0.001
2010	−0.035	0.010	11.6	<0.01
2011		Reference		
Volume				
≥100 patients/y	−0.345	0.014	612.8	<0.001
75–99 patients/y	−0.089	0.012	60.8	<0.001
50–74 patients/y	0.050	0.010	26.7	<0.001
25–49 patients/y	0.037	0.008	21.0	<0.001
5–24 patients/y	0.097	0.007	190.7	<0.001
<5 patients/y		Reference		
Factor				
Baseline NIHSS	−0.002	0.001	15.0	<0.001
Female sex	0.019	0.005	13.8	<0.001
Diabetes mellitus	0.009	0.007	1.9	0.17
Hypertension	0.026	0.005	22.8	<0.001
Atrial fibrillation	0.011	0.006	3.3	0.07
Previous stroke	0.029	0.008	14.7	<0.001
Joined 2003–2005	−0.077	0.011	45.6	<0.001
Joined 2006–2008	−0.087	0.012	56.1	<0.001
Joined 2009–2011		Reference		

Positive values of β coefficient means longer and negative values shorter door-to-needle times. Note the magnitude of β coefficients and Wald χ^2. NHISS indicates National Institutes of Health Stroke Scale.

Table 3. Generalized Estimating Equations Model for the Centers That Joined During 2003

Parameter	β	SE	Wald χ^2	*P* Value
Year				
2003	0.241	0.027	79.4	<0.001
2004	0.189	0.026	52.8	<0.001
2005	0.113	0.024	21.7	<0.001
2006	0.081	0.025	10.3	<0.01
2007	0.116	0.025	21.2	<0.001
2008	0.019	0.026	0.6	0.46
2009	0.027	0.025	1.2	0.27
2010	0.038	0.025	2.2	0.14
2011		Reference		
Volume				
≥100 patients/y	−0.401	0.021	349.5	<0.001
75–99 patients/y	−0.109	0.021	27.7	<0.001
50–74 patients/y	0.277	0.017	282.5	<0.001
25–49 patients/y	0.183	0.013	186.4	<0.001
5–24 patients/y	0.178	0.014	158.0	<0.001
<5 patients/y		Reference		
Factor				
Baseline NIHSS	−0.003	0.001	8.3	<0.01
Female sex	0.019	0.009	3.9	<0.05
Diabetes mellitus	0.001	0.013	0.01	0.94
Hypertension	0.013	0.010	1.7	0.19
Atrial fibrillation	0.011	0.011	1.0	0.32
Previous stroke	0.031	0.013	5.7	0.02

Positive values of β coefficient means longer and negative values shorter door-to-needle times. Note the magnitude of β coefficients and Wald χ^2. NHISS indicates National Institutes of Health Stroke Scale.

mostly from large centers that joined the registry between 2003 and 2005: Tables I and II in the online-only Data Supplement). In most centers, DNT tended to rise after 2009/2010, except for centers treating ≥100 patients/y (Figures 1 and 2). This increase of DNT observed after 2009 can be perhaps explained by publication of the European Cooperative Acute Stroke Study (ECASS)-III trial and SITS-ISTR study at the end of the year 2008,[10,11] which led to extension of the time window for stroke thrombolysis from 3 to 4.5 hours. The implementation

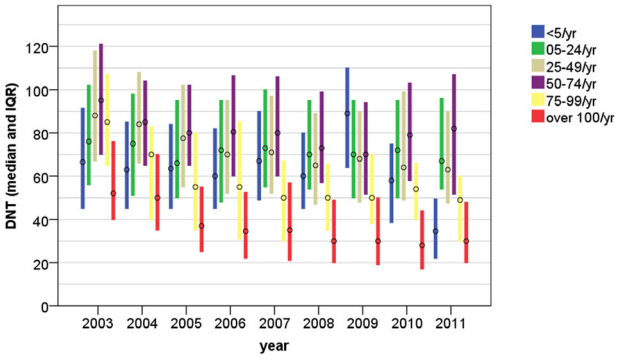

Figure 2. Temporal changes in door-to-needle time (DNT and interquartile range) in centers that started registration within 2003 at the center level.

of the extended time window followed gradually in different countries and centers. Evidence from UK SITS patients suggests that extension of the time window led to treatment of more patients who may otherwise have missed the window for treatment, but also possibly a relaxation of urgency,[12] which was also shown in our recent analysis.[13] In contrast, Messé et al[14] found that publication of the ECASS-III trial did not lead to longer DNT in Get With The Guidelines.

Taken together, our data confirmed that experience is more robustly linked to high annual volume of patients than to the year of treatment. Such effect of volume is not only unique for stroke thrombolysis[9,15] but is also seen in other scenarios.[16–19] We have recently described measures that led to reduction of DNT in the Helsinki Center,[20,21] where the current median DNT is 20 minutes. In the Barnes-Jewish Hospital in St. Louis, reduction of DNT was achieved after implementation of value stream analysis of Toyota's lean manufacturing principles.[22] In this study, we observed that DNT was associated with annual volume of patients, sex, history of hypertension and previous stroke, and baseline NIHSS, findings similar to Get With The Guidelines.[9] In another analysis of Get With The Guidelines, Xian et al[23] reported 3 hospital strategies independently associated with lower DNT: rapid triage/stroke team notification, single-call activation system, and tissue-type plasminogen activator stored in the emergency department.

Results of the study presented here suggest that learning and experience in delivering thrombolysis in a timely fashion are transferrable. Also, many centers have made little progress in reducing DNT during the past 10 years. On the basis of these findings, we decided to launch a global project aiming to reduce DNT: Reduction of In-hospital Delays in Stroke Thrombolysis (SITS-WATCH). In the pilot phase of the project, we sent an itemized questionnaire to the SITS centers. This pilot phase helped us to understand the local situation and to recognize the factors prolonging DNT in the SITS centers. In the next phase, we sent specific tasks to the participating centers, via implementation of which it is possible to reduce DNT. Clearly, factors like rural versus urban, academic versus community-based, public versus private settings, availability of neurological and radiological expertise, level of emergency medical services expertise, prenotification, and many others do most probably play a role. The SITS-WATCH project is registered under its name at http://www.clinicaltrials.gov (NCT01811901). A similar initiative Target: Stroke is organized by the American Heart Association/American Stroke Association.[24]

Our study has limitations. We did not extract safety data (symptomatic intracranial hemorrhage) for the purpose of this study. However, safety data were described in other SITS publications.[25] In the Helsinki center, the continuous decline in DNT was achieved without an increase in the rate of hemorrhagic complications.[20] Furthermore, we do not present any outcome data, as relationship between shorter treatment delays and better functional outcome was addressed elsewhere.[1,3,4] Our data come mostly from European centers, which is an important issue on generalizability of our findings to other countries with varying systems of stroke care. Last but not least, the SITS registry includes patients based on voluntary registration of participating centers, which might have caused a selection/referral bias.

To conclude, only minor overall improvements in DNT were observed during the first decade of the SITS registry. About experience, center volume is more important than the year of treatment. Hence, a multicenter project to reduce DNT focusing mostly on the centers with lower annual volume is warranted. We think such a project is feasible. As an example, the Helsinki experience was used in the Melbourne center, where the in-hours median DNT dropped from 43 (33–59) minutes to 25 (19–48) minutes in 4 months after implementation of the changes.[26] Because Melbourne is a single and a dedicated stroke center and we do not have the data on DNT in centers not participating in the SITS, we cannot anticipate that DNT would fall to such low levels in other centers. Substantial changes can nonetheless be achieved.

Disclosures

Dr Ahmed is an employee of Safe Implementation of Thrombolysis in Stroke (SITS) International, which received a grant from Boehringer-Ingelheim and Ferrer for the (SITS Monitoring Study) SITS-MOST and SITS-International Stroke Thrombolysis (ISTR). Dr Wahlgren has received expenses from Boehringer-Ingelheim for his role as a member of the steering committee of the ECASS-III trial, has served as a consultant to Thrombogenics as the chairman of the data safety monitoring board, and has received lecture fees from Boehringer-Ingelheim and Ferrer. SITS International (chaired by Dr Wahlgren) received grants from Boehringer-Ingelheim and Ferrer for SITS-MOST and SITS-ISTR. Dr Wahlgren's institution has also received grant support toward administrative expenses for coordination of the ECASS-III trial. Dr Lees serves on the data monitoring committees for trials sponsored by Boehringer-Ingelheim, Grifols, and Lundbeck and has received fees and expenses from Boehringer-Ingelheim for lectures; his department has received research grant support from Genentech. Dr Toni serves as a consultant for Boehringer-Ingelheim and received speaker honoraria from Boehringer-Ingelheim, Sanofi-Aventis, and Pfizer Inc. Dr Roffe is a board member of EMTensor, serves as a consultant for Lundbeck, and has received lecture fees and expenses form Boehringer, Bayer, Johnson and Johnson, Covidien, and Sanofi. Her research team has had the benefit of consumables provided by Phagenesis, Codman, Acandis, EV3, and Concentric Medical. Dr Tatlisumak received research grant support from Boehringer-Ingelheim (modest), Boehringer-Ingelheim Sanofi Aventis (significant), H. Lundbeck A/S, Mitsubishi Pharma, PhotoThera, and BrainsGate; he is a consultant/advisory board member (modest) of Boehringer-Ingelheim, Bayer, Pfizer, Mitsubishi Pharma, and BrainsGate; and he is speaker's bureau member (modest) of Boehringer-Ingelheim, Bayer, and Professio Oy. The other authors report no conflicts.

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Trends in Door-to-Thrombolysis Time in the Safe Implementation of Stroke Thrombolysis Registry: Effect of Center Volume and Duration of Registry Membership

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SUPPLEMENTAL MATERIAL

Trends in door-to-thrombolysis delays in the SITS registry: effect of center volume and duration of registry membership

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Supplementary Table I. Test of model effects when including interaction between center volume and year of treatment

Parameter	Robust Wald $\chi 2$	degree of freedom	P-value
Year of treatment	141.56	8	<0.001
Center volume	974.76	5	<0.001
Female gender	19.91	1	<0.001
Diabetes mellitus	2.51	1	0.11
Hypertension	32.84	1	<0.001
Atrial fibrillation	4.09	1	<0.05
previous stroke	16.56	1	<0.001
baseline NIHSS	13.08	1	<0.001
center volume*year of treatment interaction	588.62	40	<0.001

Supplementary Table II. Parameter estimates from the interaction model

Parameter	B	Standard error	p-value
Year 2003	-0.115	0.029	<0.001
Year 2004	-0.134	0.024	<0.001
Year 2005	-0.154	0.023	<0.001
Year 2006	-0.181	0.024	<0.001
Year 2007	-0.117	0.025	<0.001
Year 2008	-0.055	0.028	<0.05
Year 2009	-0.006	NA	NA
Year 2010	-0.009	NA	NA
Year 2011		Reference	
< 5 patients / year		Reference	
5-24 patients / year	0.018	0.024	0.47
25-49 patients / year	-0.085	NA	NA
50-74 patients / year	0.062	0.033	0.059
75-99 patients / year	-0.090	0.044	<0.05
≥ 100 patients / year	-0.771	0.041	<0.001
baseline NIHSS	-0.002	0.0005	<0.001
female gender	0.020	0.005	<0.001
Diabetes mellitus	0.010	0.007	0.113
Hypertension	0.026	0.005	<0.001
Atrial fibrillation	0.012	0.006	<0.05
Previous stroke	0.031	0.008	<0.001
	INTERACTIONS		
≥ 100 patients*2003	0.621	0.073	<0.001
≥ 100 patients*2004	0.716	0.064	<0.001
≥ 100 patients*2005	0.477	0.057	<0.001
≥ 100 patients*2006	0.505	0.058	<0.001
≥ 100 patients*2007	0.502	0.056	<0.001
≥ 100 patients*2008	0.389	0.056	<0.001
≥ 100 patients*2009	0.323	NA	NA
≥ 100 patients*2010	0.214	NA	NA
≥ 100 patients*2011		Reference	
75-99 patients*2003	0.372	0.098	<0.001
75-99 patients*2004	0.102	0.073	0.16
75-99 patients*2005	0.109	0.059	0.063
75-99 patients*2006	0.078	0.054	0.15
75-99 patients*2007	-0.060	0.054	0.27
75-99 patients*2008	-0.092	0.054	0.09
75-99 patients*2009	-0.164	NA	NA
75-99 patients*2010	-0.141	NA	NA
75-99 patients*2011		Reference	
50-74 patients*2003	0.232	0.059	<0.001
50-74 patients*2004	0.104	0.046	<0.05
50-74 patients*2005	0.049	0.045	0.27
50-74 patients*2006	0.049	0.041	0.24

50-74 patients*2007	-0.069	0.041	0.09
50-74 patients*2008	-0.109	0.042	<0.01
50-74 patients*2009	-0.179	NA	NA
50-74 patients*2010	-0.140	NA	NA
50-74 patients*2011		Reference	
25-49 patients*2003	0.362	NA	NA
25-49 patients*2004	0.308	NA	NA
25-49 patients*2005	0.250	NA	NA
25-49 patients*2006	0.207	NA	NA
25-49 patients*2007	0.158	NA	NA
25-49 patients*2008	-0.010	NA	NA
25-49 patients*2009	-0.027	NA	NA
25-49 patients*2010	-0.025	NA	NA
25-49 patients*2011		Reference	
5-24 patients*2003	0.091	0.050	0.068
5-24 patients*2004	0.139	0.037	<0.001
5-24 patients*2005	0.090	0.031	<0.01
5-24 patients*2006	0.129	0.031	<0.001
5-24 patients*2007	0.047	0.031	0.12
5-24 patients*2008	0.002	0.032	0.96
5-24 patients*2009	-0.057	NA	NA
5-24 patients*2010	-0.015	NA	NA
5-24 patients*2011		Reference	
<5*for all years		References	

Note: In the presence of interaction term, the marginal effect estimates for center volume and year of treatment cannot be directly converted into time units.
NA: Could not estimate due to low number of observations per category.