Is comparative effectiveness research effective? Abandonment of high dose chemotherapy/hematopoietic cell transplants for breast cancer

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Abstract: We examine the impact of negative clinical trial results on use of autologous hematopoietic cell transplantation (HDC/HCT) in breast cancer patients. Abandonment of occurred rapidly; one year after the results became public, volume was 20% of the 1998 peak. Teaching and research hospitals were slower to discontinue the procedure, and the pattern of decline suggests that hospitals passively abandoned HDC/HCT as demand declined rather than actively deciding to discontinue offering HDC/HCT to patients.

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1. INTRODUCTION

Congress recently appropriated substantial sums for comparative effectiveness research. Comparative effectiveness research is often touted as a vehicle to reduce costs, but theoretically, the impact of comparative effectiveness research on spending is ambiguous. If studies tend to find that the most expensive option is also the most effective, spending will increase.

Presumably, the National Institutes of Health and other federal sponsors will avoid this outcome by prioritizing studies of widely used, costly interventions where there is a strong *ex ante* presumption that the intervention is no better than a less costly alternative (Congressional Budget Office 2007; VanLare JM et al. 2010). Assuming that studies bear out sponsors' prior beliefs, the potential for comparative effectiveness research to reduce costs depends on its impact on practice patterns.

In the US, there is no formal mechanism to incorporate the findings of comparative effectiveness research into clinical practice. Adoption of recommended practices depends on the independent decisions of thousands of physicians, patients and employers and hundreds of insurers. There are a number of factors that promote adoption of new, on-patent technologies, including fee-for-service reimbursement, marketing, patients' and physicians' faith in technological progress, and the malpractice system (Emanuel and Fuchs 2008). These same factors may work against abandonment of existing technologies, so that the reaction to positive and negative findings is asymmetric.

In this paper we examine the abandonment of high dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDC/HCT) for women with breast cancer.[1] Initially, technology evaluations by the Blue Cross and Blue Shield Association and other groups raised concerns about the value of the procedure, but matters remained unsettled through the 1990s until randomized clinical trials demonstrated that the procedure was no better than standard outpatient chemotherapy. Although results from the trials were released over 10 years ago, it is useful to revisit this example in light of the current debate over comparative effectiveness research and its potential impact on costs.

2. COMPARATIVE EFFECTIVENESS RESEARCH OF HDC/HCT

High dose chemotherapy followed by autologous blood and marrow transplantation entails: 1) harvesting and storing hematopoietic stem cells (HSC)

obtained directly from the patients' bone marrow or peripheral blood after hematopoietic growth factor +/- chemotherapy mobilization, 2) administering high doses of chemotherapy with the intent of killing malignant cells but with the recognition that healthy marrow cells would also be destroyed, and 3) transplanting the stored HSC back into the patient to regenerate hematopoiesis. The story of how HDC/HCT came to be widely used as a treatment for breast cancer despite the absence of evidence of efficacy has been previously recounted in Rettig et al.'s *False Hope* (2007). Briefly, the first HDC/HCT in women with breast cancer were performed in the late 1970s, but the procedure did not come into widespread use until the late 1980s and early 1990s (Antman and Gale 1988). Initially, HDC/HCT was used in women with metastatic disease, but, by

the mid 1990s about half of HDC/HCTs were performed in women with less advanced (stage II and III) malignancies (Rettig et al. 2007, p. 147).

For women with few curative treatment options, HDC/HCT offered the hope of long-term survival, but, because of its cost, side effects, the large number of potentially eligible patients with this common malignancy, and limited evidence of efficacy, the procedure was subject to a high degree of scrutiny from insurers. Many initially refused to pay for the procedure on the grounds that it was investigational. Non-coverage was the subject of a number of lawsuits in the 1990s brought by patients against insurers (Mello and Brennan 2001), and 11 states[2] eventually mandated that insurers cover HDC/HCT.

Table 1 shows a timeline of the major studies and technology evaluations of HDC/HCT as a treatment for breast cancer from the early 1980s to the end of the 1990s. Uncontrolled studies reporting tumor response rates provided the first evidence of the potential for HDC/HCT. There soon followed a series of evaluations sponsored by the Blue Cross and Blue Shield Association. These concluded that there was insufficient evidence to recommend HDC/HCT over conventional therapy (for example, see Eddy 1992).

In 1993, oncologist William Peters and colleagues published a study showing that women with stage II or III tumors treated with HDC/HCT had higher event-free survival rates compared to historical controls (Peters et al. 1993). However, an unpublished 1994 Blue Cross and Blue Shield Association evaluation re-affirmed the previous reports: HDC/HCT should be considered an experimental therapy without proven efficacy.

In 1995 South African investigators published a randomized controlled trial of HDC/HCT versus conventional chemotherapy reporting higher survival rates for women with metastatic disease treated with HDC/HCT versus conventional therapy (Bezwoda et al. 1995). The trial (which was later found to be fraudulent), combined with evidence of decreasing regimen-related mortality, led to a growing acceptance of HDC/HCT among patients and physicians. Several US multisite trials of HDC/HCT began enrolling patients in the 1990s, but patients were reluctant to enroll. HDC/HCT was widely available to patients outside of clinical trials and many did not want to risk being randomized to the standard care arm. Less than 10% of women who received HDC/HCT in the 1990s were enrolled in a randomized controlled trial.

A Dutch trial, published in the *Lancet* in August 1998 (Rodenhuis et al. 1998), found no difference in progression free and overall survival between patients treated with HDC/HCT versus conventional therapy. However, matters remained unsettled until May 1999, when investigators presented results showing no overall survival advantage for women receiving HDC/HCT from three randomized controlled trials – two from the US and one from Sweden – at the annual meeting of the American Society of Clinical Oncology (ASCO). A fourth trial from South Africa, which was also presented at the May 1999 meeting, reported a survival advantage for patients in the HDC/HCT arm. A subsequent investigation determined that the principal investigator had manufactured the data for this study and the previously published South African trial.

Initially, many oncologists and transplanters reacted cautiously to the negative trial results. Some believed that specific subgroups of patients (for example, women with inflammatory breast cancer) might still be good candidates for HDC/HCT, and proponents of HDC/HCT noted that results were "preliminary". The American Cancer Society released a statement in (Schellenbach 1999) stating

> The American Cancer Society strongly supports reimbursement for bone marrow transplantation by insurance carriers for the treatment of appropriate hematologic malignancies. We believe that there is currently insufficient evidence to determine the efficacy of bone marrow transplantation for breast cancer, and support further analysis of clinical data obtained from carefully controlled peer-reviewed clinical trials.

Despite these admonitions, use of the procedure declined steeply.

3. Abandonment of medical treatments

There is an extensive literature on the adoption and diffusion of new health care technologies. Comparatively few studies examine abandonment, or "relinquishment", of widely used drugs and procedures following the publication of negative results (Rye and Kimberly 2007). These find that practice patterns change slowly in response to negative results and abandonment is less than complete.

Intermittent positive pressure breathing as a treatment for chronic obstructive pulmonary disease was the subject of a number of studies, including a National Heart, Lung, and Blood Institute clinical trial published in 1983 questioning the value of the therapy (The IPPB Trial Group 1983). By 1986 use was about 50 percent of the 1983 level (Duffy and Farley 1992). The number of hospitals offering intermittent positive pressure breathing declined from 37 in 1983 to 23 in 1986. The timing of abandonment was unrelated to teaching status, the proportion of board-certified physicians, or size.

The ALLHAT trial found that the alpha-blocker doxazosin was associated with substantially higher rates of adverse cardiovascular events in hypertensive patients (Pressel et al. 2001). Three years after ALLHAT, the number of doxazosin prescriptions was 78 percent of the 1999 peak (Stafford et al. 2004).

Negative results from the Heart and Estrogen/Progestin Replacement Studies of hormone replacement therapy were widely publicized. Two years after the publication of the second trial the number of prescriptions was 62% of the peak (Hersh et al. 2004). The rate and magnitude of decline was greater in regions with more media coverage of the trials (Haas et al. 2007).

Publication of studies in the mid 1990s linking use of calcium channel blockers in patients discharged from the hospital after acute myocardial infarction to adverse events led to relatively steep declines in use over a three year period, with post-study prescription rates equal to one-quarter of the peak (Majumdar et al. 2001). Rates of abandonment were similar between cardiologists and generalists.

4. ABANDONMENT OF HDC/HCT

We analyzed the rate and pattern of abandonment of HDC/HCT for breast cancer using data from the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a voluntary consortium involving more than 500 transplant centers in 54 countries.[3] For this analysis, we used patient level data on 15,847 HDC/HCT performed in the US for women with a primary diagnosis of breast cancer that were reported to the CIBMTR from 200 transplant centers between 1994 and 2005. The CIBMTR estimates that it collected data on 60 percent of autologous hematopoietic stem-cell transplant procedures performed in the US during this time period.

4.1 Aggregate use

Monthly counts of the number of women undergoing HDC/HCT and reported to the CIBMTR registry are displayed in Figure 1.[4] After rising rapidly through 1997, the number of cases started to decline in early 1998, dropping rapidly after the May 1999 ASCO meeting. The decline in use of HDC/HCT beginning in early 1998 may have been a reaction to the August 1998 publication of the Dutch trial (Rodenhuis et al. 1998), which reported negative results in a sample of women with non-metastatic tumors. Results of the trials presented at the May 1999 ASCO meeting were publicized prior to the meeting – NBC news ran a story about the studies on March 9, 1999 – but it is unlikely that the results were known prior to 1999.

By one year after May 1999, the number of HDC/HCTs was less than 20 percent of the March 1998 peak.[5] Still, physicians did not discontinue HDC/HCT overnight. Over 1,500 women received HDC/HCT in the two years after May 1999. Some or many of these women were enrolled in ongoing clinical trials.

4.2 Hospital-level abandonment of HDC/HCT for breast cancer patients

We considered a hospital and its physicians to have abandoned HDC/HCT if it did not perform any procedures in women with breast cancer for six consecutive months, as indicated in the CIBMTR registry. We classified the last month in which a hospital performed HDC/HCT in women with breast cancer as the exit month. We analyzed discontinuation rates in the 122 hospitals that performed one or more HDC/HCT procedures in women with breast cancer between 1995 and 1997, performed more than 10 HCT procedures overall between 1995 and 2005, and were performing HDC/HCT procedures in women with breast cancer in 1998. For the sake of explication, we characterize abandonment as a decision undertaken by hospitals. In reality, the abandonment decision is a joint decision by hospital administrators and physicians.

Hospitals' abandonment of HDC/HCT is represented by the Kaplan-Meier curve in Figure 2. The height of the curve (the solid line) indicates the proportion of hospitals continuing to perform HDC/HCT in women with breast cancer. About 20 percent of hospitals performing HDC/HCT exited the market prior to May 1999. Some of these exits may have been due to physicians' premonitions about the forthcoming trial results, others reflect the natural ebb and flow of hospitals in and out of the HCT market.

The pace of exit increased in May 1999, as indicated by the divergence between the Kaplan-Meier curve and the dotted line, representing the pre-May 1999 trend. By May 2001, only a handful of hospitals were performing HDC/HCT in women with breast cancer on a regular basis.

Table 2 shows the association between selected hospital characteristics and the median time to exit in months. Note that there is substantial overlap between the categories (for example, 12 of the 19 phase III trial sites are comprehensive cancer centers). The median time to exit, measured from January 1999, among all 122 hospitals was 15 months. Among the 19 hospitals that enrolled patients in the phase III trials presented at the May 1999 ASCO meeting (which showed the procedure was ineffective) the median time to exit was 21 months. Figure 3 displays the Kaplan-Meier curves for hospitals that did and did not participate in the phase III trials.

National Cancer Institute Comprehensive Cancer Centers and teaching hospitals (as measured by membership in the Council of Teaching Hospitals) were slower to abandon HDC/HCT, though differences in median exit times are not significant. These findings are somewhat surprising given that these hospitals produce, and thus ought to be more responsive to, new medical knowledge and research. However, this observation is consistent with previous work on hospitals' abandonment of intermittent positive pressure breathing. Some of these centers may have continued to enroll patients in clinical trials that were opened prior to May 1999, believing that these studies would address questions left unanswered by the results presented at the ASCO meeting. Additionally, hospitals' decisions may have been influenced by physicians whose careers were closely tied to the continuation of research on HDC/HCT in women with breast cancer.

Hospitals located in one of the 11 states with insurance benefit mandates for HDC/HCT abandoned HDC/HCT at similar rates to hospitals in non-mandate states. Mandates did not reduce the responsiveness of medical practice to new evidence in this case.

Concern about a lack of external validity may discourage physicians from abandoning treatments following a negative trial result. Providers with better-than-average outcomes may believe that their patient selection and treatment protocols are superior to those tested in the trial. We tested this hypothesis in the context of HDC/HCT by comparing exit rates based on historical, hospital-level outcomes. We hypothesized that hospitals with better-than-average outcomes would be slower to abandon the procedure. We measured hospital-level outcomes for HDC/HCT by calculating one-year survival rates for women treated between 1995 and 1997, standardized by cancer stage (metastatic versus other). Exit rates were similar between hospitals with low and high survival rates, suggesting that historial outcomes did not influence the abandonment decision.

We measured each hospital's HDC/HCT and HCT volume (including autologous and allogenic procedures and transplants for women with breast cancer and patients with other diagnoses) based on transplants performed between 1995 and 1997 and classified hospitals as above or below the median. Hospitals that performed more HDC/HCT procedures and more HCT procedures overall were slower to abandon HDC/HCT. Hospitals that were more dependent on HDC/HCTs for their overall HCT volume, as

indicated by the share of HCTs performed in breast cancer patients, abandoned HDC/HCT at similar rates to hospitals with below-median HDC/HCT shares.

In multivariate analysis (see the Appendix), we found that hospitals' share of HCTs performed in breast cancer patients was positively related to the month of abandonment. HCT volume remained a significant predictor of the timing of abandonment, while HDC/HCT volume was not a significant predictor. After controlling for volume, National Cancer Institute Comprehensive Cancer membership was unrelated to the timing of abandonment.

4.3 Mechanism of abandonment

The previous section presumes that hospitals' medical staff offices and transplant specialists actively decided when to abandon HDC/HCT. However, it is possible that hospitals and specialists are passive actors in the process, with the decision to abandon a procedure occurring only after demand by patients and referring physicians has evaporated. Consider the different patterns of abandonment displayed in Figure 4. The top dashed line, labeled "Active", illustrates the trend in procedure volume we would expect to see if the abandonment decision was made exclusively by hospitals. In this scenario, volume is steady and then drops precipitously once the hospital decides to stop offering HDC/HCT. The bottom dashed line, labeled "Passive", illustrated the trend we would expect to see if patients and referring physicians, rather than hospitals, decide to abandon the procedure. In this scenario, volume declines steadily, reflecting diffusion of the negative results in the community, until it reaches zero, at which time the hospital has effectively, if not purposely, abandoned the procedure.

To test which of these scenarios best describes the hospital-level pattern of decline in HDC/HCT volume, we estimated monthly trends in hospital-level HDC/HCT volume using negative binomial regression. The model included a time trend variable and an indicator variable for the month before the hospital stopped performing HDC/HCT. We included in our estimation sample each hospital's procedure count in the 24 months prior to abandonment. The predicted path of decline based on the model is represented by the solid line in Figure 3. The observed pattern is somewhere between the two scenarios, but is probably closer to the "Passive" scenario. Twenty-four months prior to abandonment, average volume was 1.6 cases per month. One month prior to abandonment, volume was about 0.6 cases per month, or less than 40% of the volume two years prior.

5. DISCUSSION

The release of results showing that HDC/HCT was equivalent to conventional chemotherapy led to a rapid decline in the use of the procedure. In this respect, HDC/HCT is somewhat of an outlier; previous studies have found that practice patterns are slow to adjust to negative results. Women who underwent HDC/HCT often experienced debilitating side effects, including an elevated risk of secondary tumors (Kroger et al. 2003; Weldon et al. 2002). Following the release of the trial results, patients and referring physicians may have viewed HDC/HCT as not merely equivalent

to, but actually inferior to conventional treatment, contributing to the rapid decline in volume.

The procedure was also costly. Throughout its brief history, HDC/HCT was carefully scrutinized by insurers. However, it is unlikely that changes in coverage policy played a large role in the abandonment process. Rates of abandonment were similar in states with and without HDC/HCT coverage mandates, and Rettig et al. report that Aetna did not withdraw coverage for HDC/HCT until May 2000. Insurers' internal review processes and inability to change benefits between annual contract renewals make it difficult to rapidly incorporate negative study results into coverage policies.

Hospitals that produce new medical knowledge, i.e. teaching hospitals and National Cancer Institute Comprehensive Cancer Centers, were slower to abandon HDC/HCT. Teaching hospitals and Cancer Centers may have decided to continue to perform HDC/HCT in women with breast cancer to maintain enrollment in what were perceived as meaningful clinical trials. In general, our results suggest that most hospitals did not consciously decide to abandon the procedure. Rather, they passively abandoned HDC/HCT as demand among patients declined precipitously.

Implications for comparative effectiveness policy

Disseminate results to patients and referring physicians: Specialists may be reluctant to "give up" on cutting edge procedures, and negative results often prompt physicians to improve upon, but not abandon, technologies perceived to be innovative or cutting-edge. For example, studies reporting a lack of benefit in patients screened for lung cancer using chest X-rays begat studies of alternative screening modalities. The cycle of innovation, analysis, and refinement is an important component of medical progress, but it should not be allowed to continue indefinitely in the absence of evidence of effectiveness. When comparative effectiveness research provides clear evidence of inferiority, the government and insurers can facilitate translation and uptake by disseminating findings directly to patients and referring physicians rather than relying on specialists to discontinue performing procedures in which they are professionally and financially invested.

Counter data with more data: Prior to the release of results from the randomized controlled trials, uncontrolled studies purporting to show benefits for HDC/HCT were more persuasive to clinicians and patients than technology evaluations pointing out the limitations of these studies. The experience of HDC/HCT suggests the best way to counter less robust evidence is with additional data, which may entail performing randomized controlled trials or carefully-controlled observational studies.

Besides the obvious step of funding more studies, policymakers and the medical community can promote comparative effectiveness research by reducing the publication bias against studies that report negative results and encouraging patients to enroll in clinical trials. Because hospitals offered and payers covered HDC/HCT performed outside of randomized trials, patients were reluctant to enroll in trials and risk assignment to the standard care arm. Had the randomized controlled trials of HDC/HCT experienced more rapid patient accrual, it is likely that the results would have been available earlier than 1999.

Since the trials of HDC/HCT, institutional review boards have become more aggressive about halting trials with negative results and requiring patients considering enrolling in new studies to be informed about previously released results. If these practices had been in place in the 1990s, there may have been an earlier and steeper decline in the use of HDC/HCT. Yet, one wonders whether results from a trial that was halted early would be as persuasive to the medical community at-large and as publishable as the results from a trial that reaches its enrollment target.

Targeted comparative effectiveness research can reduce costs: Though the trials were costly, with disputes between insurers, hospitals, and the government over who should pay for them, they ultimately led to large savings. Assuming that the excess costs of HDC/HCT versus routine care are $50,000/year (Shulman et al. 2003), the trials reduced spending by at least $120 million/year, or $4 billion in present value. Prioritizing public funding of studies of costly procedures where there is a strong, *ex ante* presumption of ineffectiveness is a reasonable strategy to pursue in search of cost-savings, even if abandonment occurs slowly.

Abandonment may hinder innovation. Some oncologists continue to believe that the trials presented at the May 1999 ASCO meeting did not conclusively establish the equivalence of HDC/HCT and conventional therapy and that HDC/HCT may offer benefits for certain categories of breast cancer patients. A retrospective analysis of trial results and CIBMTR data found that while short-term survival rates were similar between women with metastatic tumors treated with standard chemotherapy versus HDC/HCT, women treated with HDC/HCT "might have a modestly higher long-term probability of survival. (Berry et al. 2002)"[6] However, the prospect of performing additional trials of HDC/HCT is dim. Demand for HDC/HCT among patients has evaporated, and presumably insurers and the National Institutes of Health have little interest in funding additional studies.

The experience of HDC/HCT raises the question: At what point should insurers and physicians "pull the plug" on a promising medical technology? Many highly beneficial procedures and treatments would have failed to gain widespread acceptance if they were subjected to clinical trials initially. It took over 50 years of painstaking trial and error before kidney transplantation came to be viewed as a non-experimental treatment for end-stage renal disease in the late 1970s. Outcomes have continued to improve dramatically even after kidney transplantation made the shift from experimental to routine use.

There is a real danger that comparative effectiveness research will squelch promising medical treatments based on substandard evidence or out-of-date treatment protocols. In the case of HDC/HCT, randomized clinical trials lacked power to detect clinically meaningful differences in outcomes. By contrast, advances in conventional chemotherapy have occurred following successive large trials designed to detect modest improvements. Of course no randomized controlled trial is perfect, and *ex post* advocates can always find flaws in trial designs that yield results at odds with their prior beliefs. Less-than-perfect evidence is a fact of life.

6. Conclusion

It is tempting to conclude that, because new drugs and procedures diffuse quickly into clinical practice, comparative effectiveness research studies that report that widely used treatments are ineffective will have an equally rapid impact on practice. However, previous work on abandonment has shown that physicians, hospitals, and patients are slow to respond to new evidence of ineffectiveness. In the case of HDC/HCT for breast cancer, release of negative results led to unusually rapid changes in practice patterns; one year after the results were released, volume was 20% of the early 1998 peak. The experience suggests that randomized controlled trials of treatments where there is an *ex ante* presumption of ineffectiveness, though costly, can yield long-run savings.

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Endnotes

[1] The terminology used to describe the procedure has changed over time. Previously, the procedure was referred to as a "bone marrow" transplant. Today, the preferred term is "hematopoietic cell" or "hematopoietic stem cell" transplant.
[2] The 11 states that enacted coverage mandates are Florida, New Hampshire, Massachusetts, Virginia, New Jersey, Tennessee, Minnesota, Missouri, Georgia, Kentucky, and Montana. See Table 6.1 in Rettig et al. for more information.
[3] Transplant centers worldwide contribute data patient characteristics and outcomes on consecutive allogeneic and autologous hematopoietic stem cell transplants to CIBMTR. Participating centers are required to report all transplants consecutively and compliance is monitored by on-site audits. Computerized checks for errors, physician review of submitted data, and on-site audits of participating centers ensure the quality of the data. Patients are followed longitudinally, with yearly follow-up.
[4] Because center reporting of autologous hematopoietic stem-cell transplantation was voluntary, we compared reporting patterns for autologous transplants for breast cancer to that of lymphoma for each center for the study period to identify centers that intermittently submitted their data to the CIBMTR. This led to the exclusion of 53 centers (486 patients) that did not submit data consistently to the CIBMTR during this period.
[5] We performed a similar analysis using the Nationwide Inpatient Sample, a nationally-representative sample of admissions at acute hospitals in the US. We selected cases with ICD-9 codes for breast cancer (179.X) and procedure codes for high dose chemotherapy (410.1 and 410.4) and used the sample weights to obtain nationally representative estimates. The number of cases was slightly larger, particularly in 1994 to 1996, but the overall trends were very similar, and so we present only the CIBMTR data here.
[6] Two relatively recent Cochrane reviews recommend against HDC/HCT as a standard treatment for breast cancer. Farquhar C, Marjoribanks J, Basser R, Lethaby A. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD003139. DOI: 10.1002/14651858.CD003139.pub2. Farquhar C, Marjoribanks J, Basser R, Hetrick SE, Lethaby A. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD003142. DOI: 10.1002/14651858.CD003142.pub2.

Figure 1: Monthly counts of HDC/HCT procedures in women with breast cancer

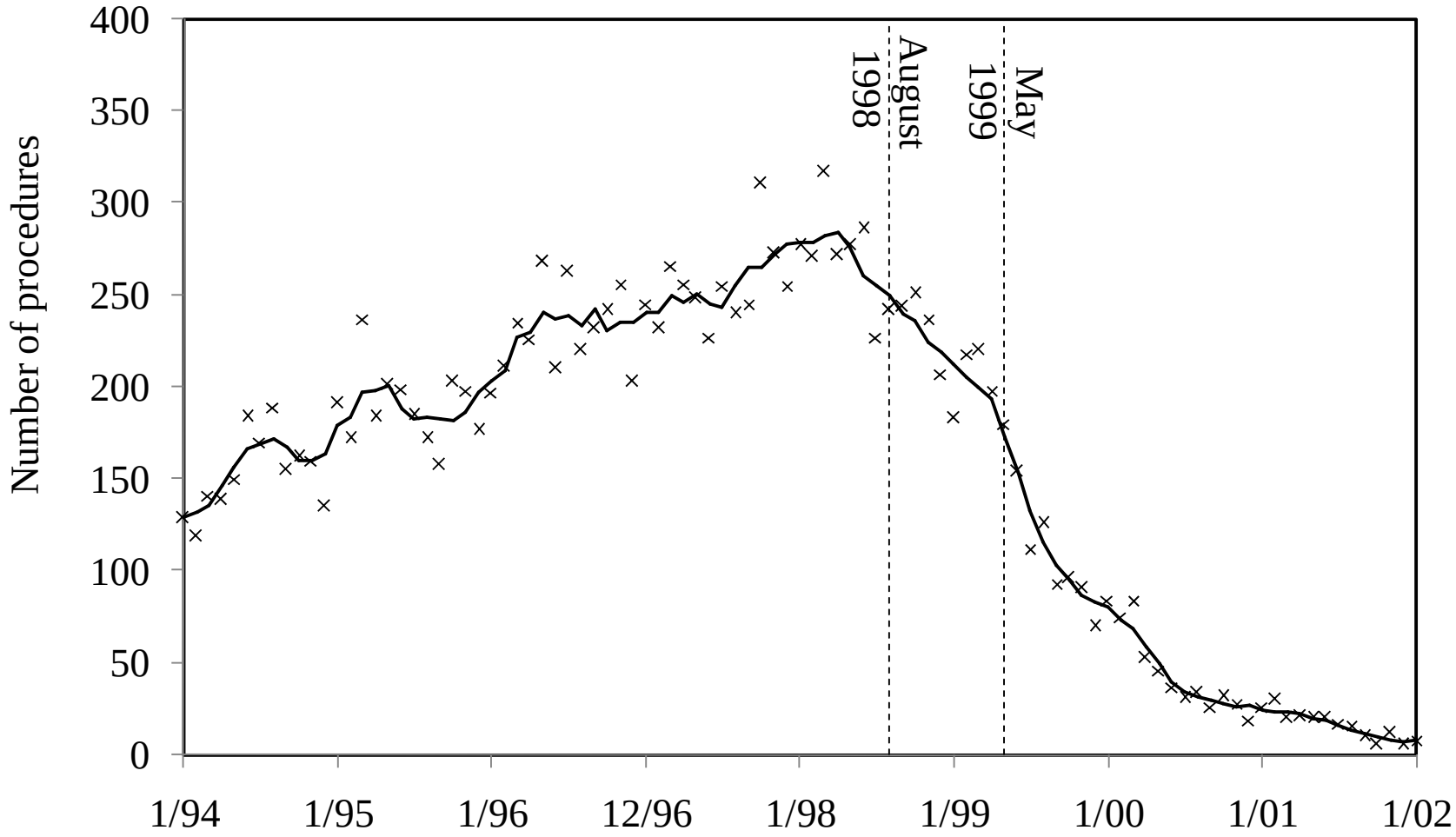
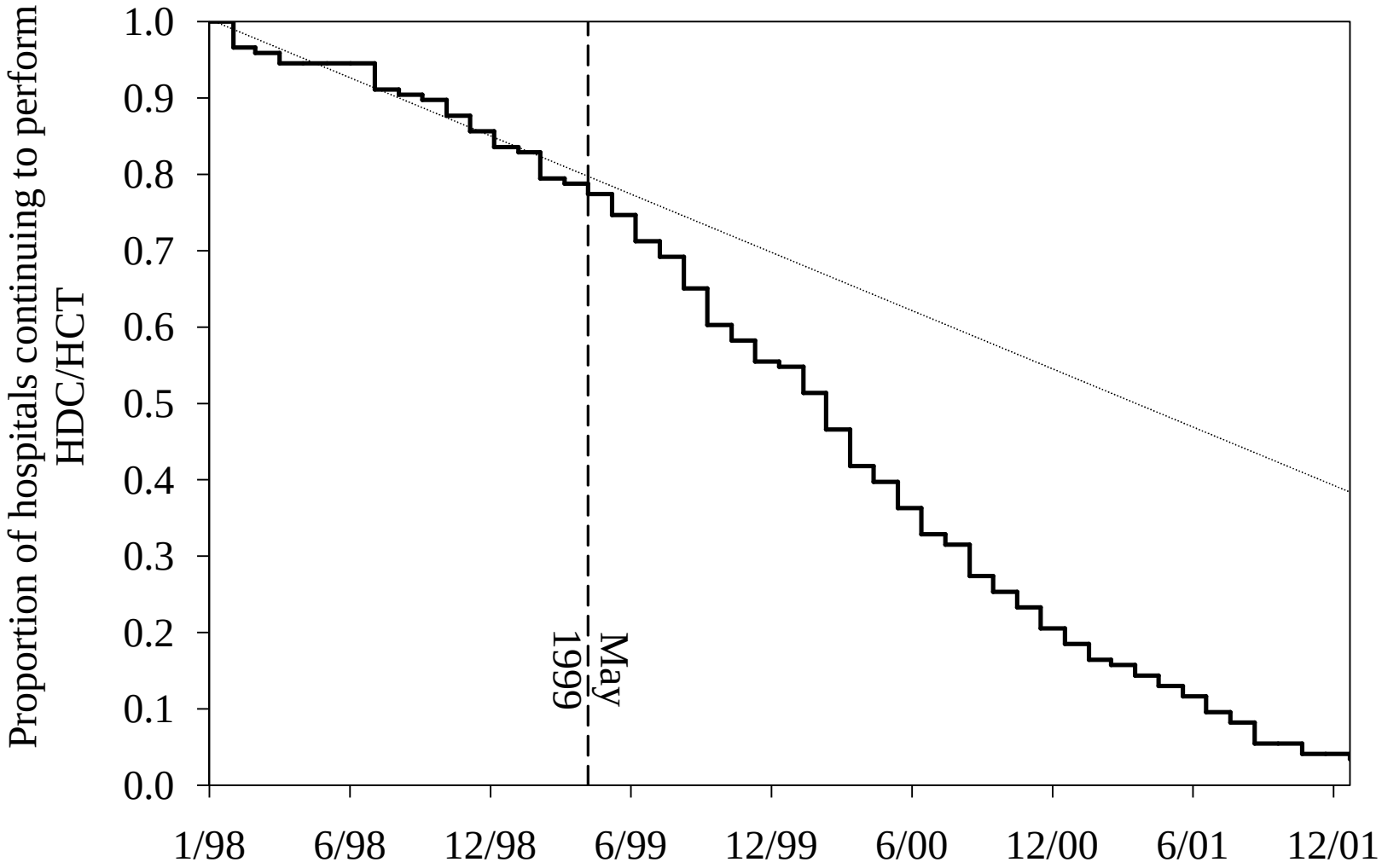


Figure 2: Kaplan-Meier curve of hospital-level abandonment of HDC/HCT



Note: The dashed line is the pre-May 1999 trend. The solid line is the Kaplain-meier curve. The sample consists of 122 hospitals.

Figure 3: Kaplan-Meier curve of hospital-level abandonment of HDC/HCT, trial sites versus other hospitals

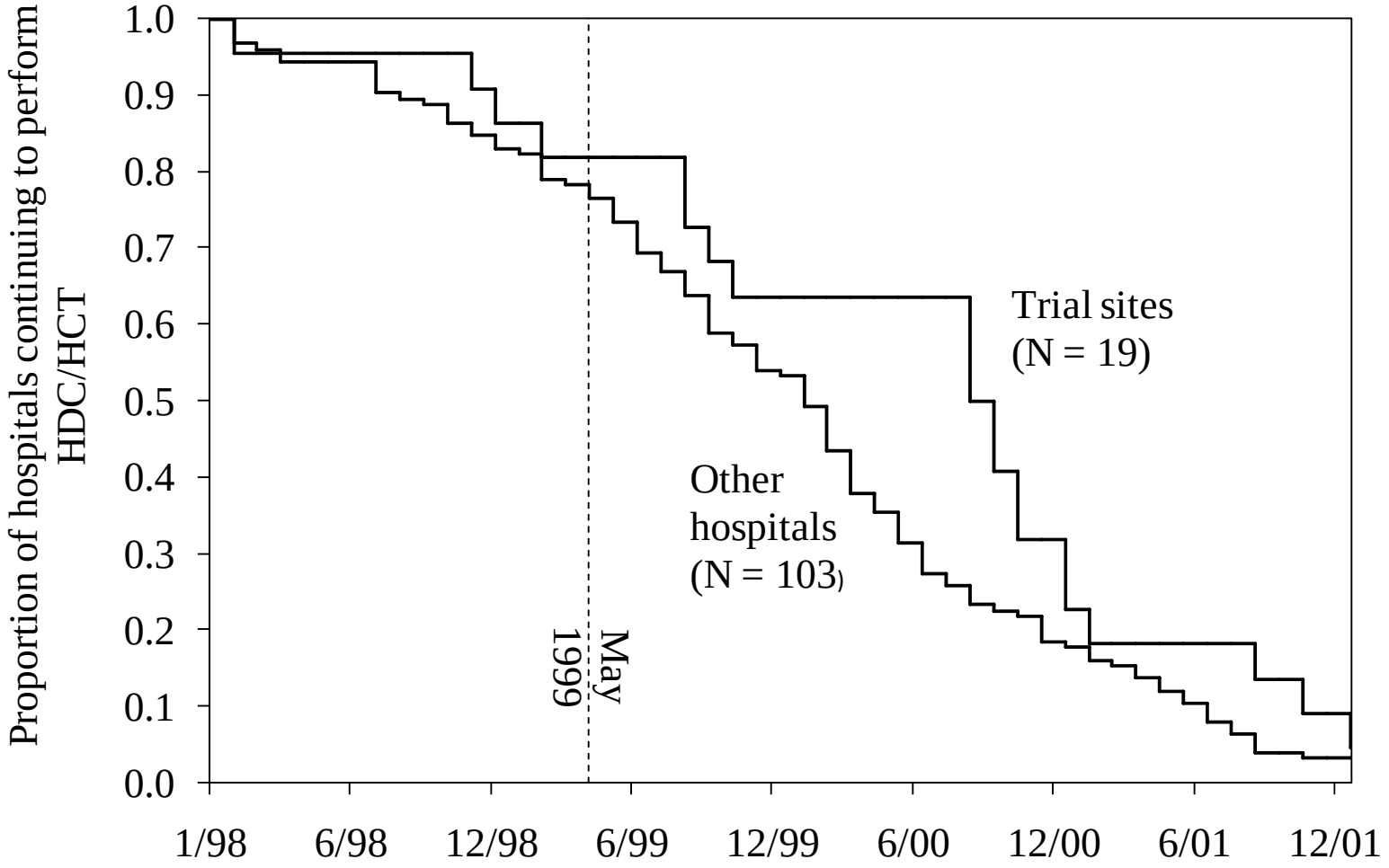


Figure 4: Pattern of hospital-level disadoption

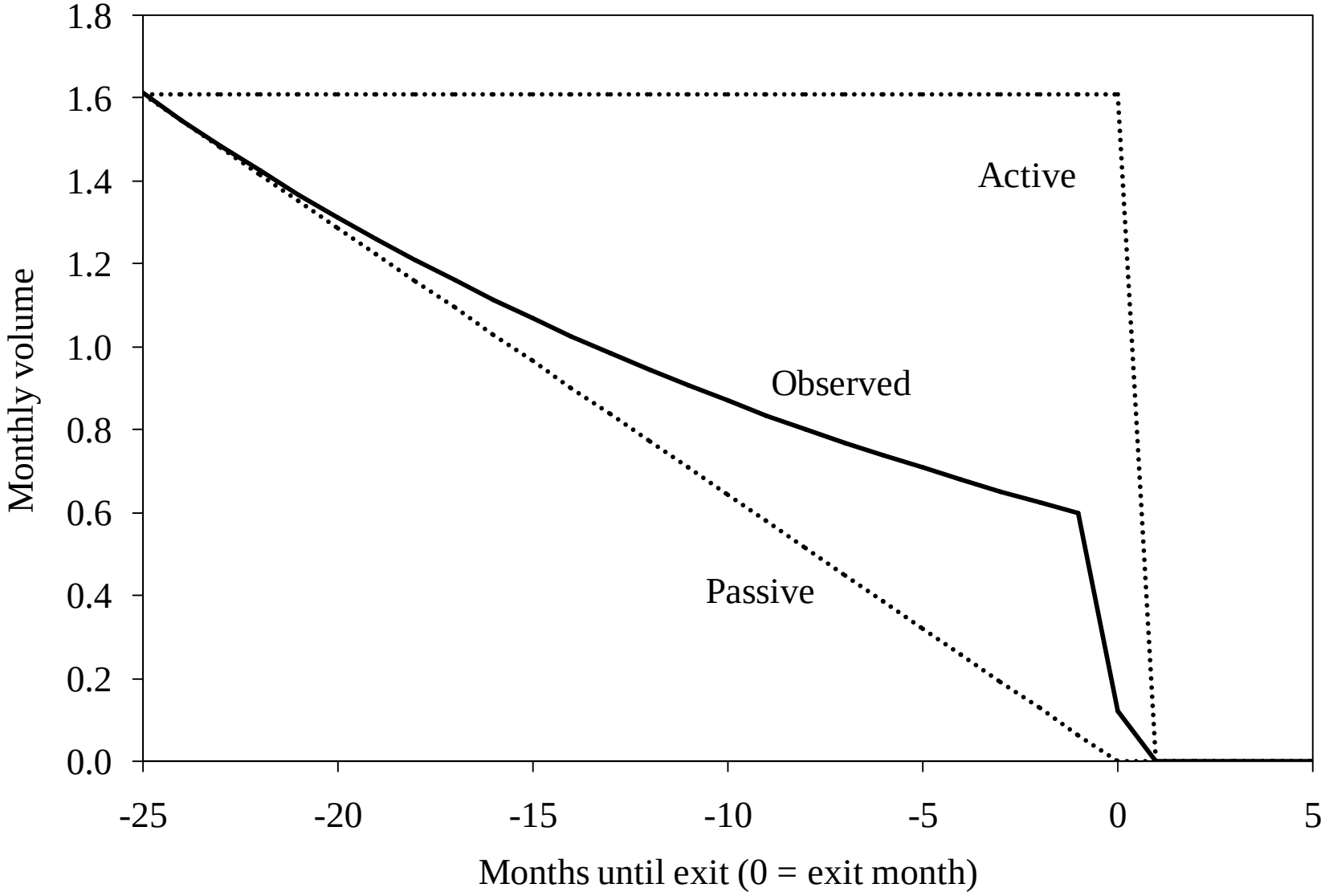


Table 1: Timeline of the major evaluations of HDC/HCT through 1999

Date	Description	Assessment[a]
1980s	Phase 2 Studies	+
1988	BCBSA technology evaluation	-
1990	BCBSA technology evaluation	-
1992	Literature review by David Eddy (1992)	-
1993	Peters et al. (1993) report benefits of HDC/HCT relative to historical controls	+
1994	BCBSA technology evaluation	-
1995	ECRI Institute: HDC/HCT "no better" than conventional therapy	-
1995	South African study showing benefits for HDC/HCT Bezwoda et al. (1995)[b]	+
1996	BCBSA technology evaluation	+
1996	NCCN guideline: HDC/HCT should be evaluated in clinical trials but is not a recommended treatment	-
October 1998	Dutch RCT published (Rodenhuis et al. 1998)	-
February 1999	Closed-door NCI meeting to review RCT results	-
March 1999	Media reports of negative RCT findings	-
May 1999	Reporting of RCTs at the annual ASCO meeting	-

[a]+HDC/HCT improves outcomes, -HDC/HCT no better than conventional care

[b]A 2000 audit found that the trial was fraudulent.

HDC/HCT: High dose chemotherapy/hemapoetic cell transplantation.
NCCN: National Comprehensive Cancer Network
BCBCA: Blue Cross Blue Shield Association
ASCO: American Society of Clinical Oncology
RCTs: Randomized controlled trials

Table 2: Impact of hospital characteristics on abandonment of HDC/HCT

Hospital characteristic	Number of hospitals	Months to exit (from 1/1/1999) Median	P-value[a]
All hospitals	122	15	N/A
Phase III trial site	19	21	0.098
Comprehensive cancer center	33	18	0.048
Teaching hospital	71	17	0.295
HDC/HCT mandate state	29	14	0.530
High HDC/HCT one-year survival rate[b]	61	15	0.833
High HDC/HCT volume (i.e., women with breast cancer)[b]	61	17	0.044
High HCT volume (i.e., breast cancer and other diagnoses)[b]	61	18	0.011
High HDC/HCT volume as a share of total HCT volume[b]	61	15	0.897

[a]Statistical significance was assessed using the log-rank test.
[b]These outcomes were measured using transplants performed during the period January 1, 1995 to December 31, 1997. The sample was split based on the median of each variable. The medians are 38% for survival, 42 for HDC/HCT volume, 95 for HCT volume, and 54% for HDC/HCT share.
HDC: High dose chemotherapy.
HCT: Hemapoietic cell transplant.
N/A: Not applicable.

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Appendix

Multivariate results for the analysis described in section 4.2

Table A1 on the next page displays estimates from Cox proportional hazards models where time to exit is the dependent variable and transplant center is the unit of observation. Consistent with the univariate analyses presented in section 4.2, the sample size is 122 hospitals.

Details of the regression model described in section 4.3

To test which of these scenarios best describes the hospital-level pattern of decline in high dose chemotherapy/bone marrow transplant volume, we estimated the following model:

$$E(y_{it}) = f(\beta_0 + \beta_1 t + \beta_2 I[t = 0]),$$

where y_{it} is the number of HDC/HCT procedures performed in hospital i in month t and t indexes time until abandonment, so t = 0 in the month of abandonment, t = -1 in the month prior to abandonment, t = -2 two months prior to abandonment, and so on. The coefficient on the indicator $I[t = 0]$ measures any sudden declines in volume between the month prior to and the month of abandonment. A finding that $\beta_1 = 0$ and $\beta_2 > 0$ would be consistent with the "Active" scenario, where hospitals suddenly decide to discontinue offering HDC/HCT. A finding that $\beta_1 < 0$ and $\beta_2 = 0$ would be consistent with the "Passive" scenario, where demand gradually declines.

We included in our estimation sample each hospital's procedure count (y_{it}) in the 24 months prior to abandonment for each hospital. The calendar months and years differ by hospital based on the time of exit. The coefficients on the intercept term, time trend, and indicator are -0.041 (SE 0.054, P = 0.448), -0.041 (SE 0.008, P < 0.001), and -1.52 (SE 0.251, P < 0.001), respectively.

We also estimated a version where we included only the 12 months prior to abandonment, but results were similar. We estimated the model using a negative binomial model. We also estimated a version with hospital fixed effects. Following the advice of Allison and Waterman (2002), we included indicator variables for each hospital rather than using the preprogrammed fixed effects negative binomial model in Stata (xtbnreg). Results were similar, and so we present estimates from the model without fixed effects.

Allison PD, Waterman R. Fixed-effects negative binomial regression models. Unpublished manuscript, 2002.

Table A1: Coefficients from a Cox-proportional hazards model of the time to exit (N = 122)

		Model 1		Model 2		Model 3		Model 4	
	Mean	OR	(SE)	OR	(SE)	OR	(SE)	OR	(SE)
Phase III trial site (%)	15	0.73	(-1.17)					0.67	(-1.31)
Comprehensive cancer center (%)	27			1.00	(0.00)			1.20	(0.59)
Teaching hospital (%)	58					1.00	(0.02)	1.00	(0.02)
HDC/HCT mandate state (%)	24	1.35	(1.32)	1.35	(1.30)	1.35	(1.31)	1.39	(1.40)
HDC/HCT one-year survival rate (%)	39	0.91	(-0.14)	0.96	(-0.06)	0.96	(-0.06)	0.93	(-0.10)
HDC/HCT volume (i.e., women with breast cancer)	59	1.00	(0.52)	1.00	(0.45)	1.00	(0.46)	1.00	(0.63)
HCT volume (i.e., breast cancer and other diagnoses)	120	0.99	(-1.74) *	0.99	(-1.63) *	0.99	(-1.71) *	0.99	(-1.83) *
HDC/HCT volume as a share of total HCT volume (%)	52	0.15	(-2.10) **	0.18	(-1.94) *	0.18	(-1.93) *	0.15	(-2.09) **

**P<0.05, *P<0.10
HDC/HCT: High dose chemotherapy/hemapoetic cell transplantation.
OR: Odds ratio.
SE: Standard error.