Fusion rate: a time-to-event phenomenon

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Object. The term “fusion rate” is generally denoted in the literature as the percentage of patients with successful fusion over a specific range of follow up. Because the time to fusion is a time-to-event phenomenon a more accurate method of representation may be made using the Kaplan–Meier method of estimation.

Methods. The current study was performed to illustrate that fusion rate is more accurately represented by median times as calculated using survival analysis. Patients undergoing a cervical decompressive corpectomy and reconstruction formed the basis of the primary analysis. A secondary analysis was made to evaluate the difference in the fusion times for one- compared with multilevel corpectomy cases.

Data were collected at a tertiary care institution over a 5-year period with 6-month follow up after the last recruitment. Descriptive statistics of baseline patient characteristics, the extent of disease, and the surgical intervention were obtained.

Fusion was the final outcome, and it was defined as the “event.” The presence of any trabeculae bridging between the vertebral body and allograft signified the occurrence of an event. Postoperative static radiographs were evaluated by independent neuroradiologists to assess the presence of fusion.

Fusion rate was determined using the Kaplan–Meier estimate. The median time to fusion was calculated, as were the 95% confidence intervals (CIs). These were stratified for patients who underwent one- and two-level vertebrectomy. The log-rank test was used to differentiate between one-level and multilevel corpectomy. Multivariate analysis was performed using Cox regression for further evaluation, by adjusting for covariates (age, sex, smoking history).

Fifty-seven patients underwent single- or multilevel corpectomy and fusion. The male/female ratio was similar, with a median age of 53 years. Fourteen patients had a history of cigarette smoking. Thirty-six patients underwent a one-level corpectomy, 20 a two-level corpectomy, and one patient underwent a three-level corpectomy. The analysis was restricted to one- and two-level cases.

The median time to fusion for the cephalad and caudad aspect of the graft–host interface was 88 days (95% CI 82–94 days) and 85 days (95% CI 77–93 days), respectively. As generally reported in the literature, this translates to a 92% (by 2.1 years) and 93% (by 1.5 years) fusion rate, for the cephalad and caudad, respectively. The median time to fusion for the cephalad aspect of the graft for one-level vertebrectomy was 87 days (95% CI 83–91 days), whereas for two-level vertebrectomy was 90 days (95% CI 59–121 days). The median time to fusion for the caudal aspect of the graft–host interface was 85 days (95% CI 80–90 days) for one-level corpectomy and 90 days (95% CI 83–97 days) for the two-level cases.

There was no statistically significant difference in the median time to fusion for one- and two-level corpectomy at either the superior or inferior aspect of the graft (p = 0.19 and 0.84, respectively). This held true even after adjusting for covariates.

Conclusions. Fusion rate is a time-to-event phenomenon and is more accurately represented using the Kaplan–Meier method of estimation.

Key Words • fusion • cervical spine • allograft • Kaplan–Meier method

Abbreviation used in this paper: CI = confidence interval.
undergoing a cervical decompressive corpectomy and reconstruction in which a fibular allograft and instrumentation were used, comprised the primary analysis. A secondary analysis was used to evaluate the difference in the fusion times for one- and multilevel corpectomy.

The study population included all consecutive patients presenting to a neurosurgical spine service at a tertiary care facility (Brigham and Women’s Hospital, Boston, MA). Data were collected from January 1995 to December 1999. Follow-up review was performed until 6 months after the last patient had been accrued to the study. Inclusion criteria included neck pain with radiological evidence of canal compromise and cord signal change, radiculopathy, or myelopathy requiring a decompressive corpectomy. Preoperative and follow-up anteroposterior and lateral plain x-ray films were required for inclusion. Patients were excluded if the cause of neurological deficit was traumatic, infectious, or neoplastic in nature and if the patient had undergone placement of posterior instrumentation. Baseline characteristics assessed were age, sex, smoking history, and number of levels of corpectomy.

Spine fusion was the final outcome. Presence of any trabeculae bridging between the vertebral body and allograft at the upper and lower aspects signified the development of an event. Negative phenomena were not included in the definition: examples of the negative events include change in the bone strut height over time, development of a kyphotic angulation over time, and development of motion at the upper and lower aspects signified the development of a graft–host interface. The analysis was restricted to data obtained in the patient facility (Brigham and Women’s Hospital, Boston, MA).

The Kaplan–Meier method of estimation was used to determine fusion rate because fusion is a time-dependent phenomenon. The median time to fusion was calculated, as were the 95% CIs. Calculations were performed for both the cephalad and caudal aspect of the graft–host interface. The analysis was restricted to data obtained in patients who underwent one- and two-level corpectomy. Survival plots were constructed. The median time to fusion for one- and two-level vertebrectomies were also evaluated separately. The log-rank test was used to determine if there was a difference in the median time to fusion for the one-level and the two-level corpectomy cases. Multivariate analysis was performed using Cox regression for additional evaluation of the fusion times, by adjusting for covariates (age, sex, smoking history). A probability value of 0.05 was chosen as the level of significance, and statistical analyses were performed using commercially available software (SPSS, Inc., Chicago, IL and JMP; SAS INstitute, Inc., Cary, NC).

### Results

The study involved 57 patients who had undergone single- or multilevel corpectomy and fusion. There were 30 men and 27 women, with a median age of 53 years (Table 1). Fourteen patients (24.6%) had a history of smoking. Thirty-six patients underwent a one-level corpectomy, 20 a two-level, and one patient underwent a three-level corpectomy. A freeze-dried fibular strut allograft was used in all cases. The types of instrumentation used included the Synthes (Oberdorf, Switzerland) Cervical Spine Locking Plate (31 cases), the Sofamor Danek (Memphis, TN) Orion locking cervical plate (23 cases), and the Sofamor Danek Atlantis Cervical Locking Plates (three cases). The rest of the analysis excluded data obtained in the patient who had undergone the three-level corpectomy.

The median time to fusion for the cephalad aspect of the graft–host interface was 88 days (95% CI 82–94 days) (Table 2 and Fig. 1). Five patients were censored from the study because they did not develop successful fusion during the follow-up period. The median time to fusion for the inferior aspect of the graft–host interface was 85 days (95% CI 77–93 days). (Table 2 and Fig. 2). Four additional cases were censored, bringing the fusion rate, as generally reported in the literature, to 92% (by 2.1 years) and 93% (by 1.5 years) for the cephalad and caudal aspect of the graft–host interface, respectively.

Results were then evaluated for each vertebrectomy level separately. The median time to fusion for the cephalad aspect of the graft for one-level vertebrectomy was 87 days (95% CI 83–91 days), whereas for two-level cases it was 90 days (95% CI 59–121 days) (Table 1 and Fig. 1). There was no statistically significant difference in the median time to fusion for one- and two-level corpectomies (p = 0.19). Five patients who underwent one-level corpectomy were censored but none undergoing two-level corpectomy. If represented as a “fusion rate,” one-level corpectomy cases would have a fusion rate of 86% (by 2.1 years), whereas the two-level corpectomy cases would have a fusion rate of 100% (by 1 year), which would appear different from the results of the log-rank statistic.

The median time to fusion for caudal aspect of the graft–host interface was 85 days (95% CI 80–90 days) for one-level corpectomy and 90 days (95% CI 83–97 days) for the two-level corpectomy (Table 1 and Fig. 2). Similar to the cephalad aspect of the graft, there was no statisti-
cally significant difference in the median time to fusion (p = 0.84), yet the fusion rates were 89% (by 1.4 years) and 100% (by 1.5 years) for the one-level and two-level cases, respectively.

There was no statistically significant difference in the median time to fusion for the cephalad aspect of the graft in one- compared with two-level vertebrectomy cases, even after adjusting for the age, sex, or smoking history of the patient (hazard ratio = 1.44, p = 0.29). Similar results were obtained in the analysis of the caudal aspect of the graft–host interface (hazard ratio = 0.89, p = 0.75).

Discussion

The current method of reporting fusion rate involves studying the number of cases with radiographically documented fusion over a fixed time period. The time period reported typically varies, as does the definition of fusion.\(^2\)-\(^{19,21-36}\) In the present study we evaluated the former concept. Unfortunately, there are multiple drawbacks to the prevailing technique of evaluating fusion rates. By addressing fusion only at a fixed point in time the actual timing of fusion is dismissed, which tends to lose information (thus power), and converts results into a yes/no outcome.\(^20\)

In addition, by using a binary outcome the results are biased by an arbitrary end point for the study follow up. Most important, if patients are followed long enough there may appear to by radiologically documented fusion in most if not all, making the analysis uninformative. A more accurate method of reporting fusion is required. Survival analysis is a statistical methodology that is used for evaluating time to event outcomes.\(^1\) This analytical method maximizes available information, because the time until fusion occurrence is used rather than presence or absence of fusion at an arbitrary study end point. Timing of information may also be obtained in patients for whom follow-up information is limited due to withdrawal from the study, if they are lost to follow-up evaluation, or if the study is completed before the final event occurs. Such cases are then censored. By presenting the fusion rate based on survival analysis, a measure of the time to fusion rather than absolute fusion rates may be obtained.

Certainly if all patients develop fusion prior to the study end point, simply reporting the median time is similar to computation using the Kaplan–Meier method of estimation.

The current study illustrates the need for a more accurate method of reporting of fusion rates. It alludes to a 3-month median time to fusion in patients who have undergone cervical corpectomy in which a fibular strut grafting and anterior instrumentation were used. Definitive conclusions about the median time to fusion would require this to be the primary outcome being evaluated and a sample size that is larger. We also noted that there was no statistically significant difference in the median time to fusion for one- and two-level corpectomies. The median time to fusion analyzed was 87 days (95% CI 83–91 days) for the superior aspect and 85 days (95% CI 80–90 days) for the inferior aspect of one-level corpectomy compared with 90 days (95% CI 59–121 days) and 90 days (95% CI 83–97 days) (superior and inferior, respectively) for two-level corpectomy. Although lack of statistical significance does not imply equivalency, the narrow and overlapping CIs certainly allude to it. If one were to use fusion rate as reported in the literature it would be 86% by 2.1 years for one-level cases and 100% by 1 year for two-level cases at the superior aspect. The fusion rate would be 89% by 1.4 years and 100% by 1.5 years for one-level and two-level cases, respectively, for the inferior aspect of the graft. This certainly would have implications quite different from those assessed by the Kaplan–Meier curves and log-rank statistic. Furthermore, as is evident, it is difficult to compare results using the literature method for reporting fusion rate because of the arbitrary follow-up times.
Fusion rates reported in the literature following cervical decompression vary from 46 to 100%, depending on whether instrumentation was used as well as the number of levels decompressed.2–12,14–18,21–36 Boni, et al.,15 performed multilevel corpectomies on 39 patients and reported that “fusion of the transplant occurred 60 to 90 days postoperatively in all cases.” Bernard and Whitecloud13 and Zdeblick and Bohlman15 also noted 100% union in 21 and 14 patients followed for 12 to 89 months and 6 months to 3.75 years, respectively. Fernyhough, et al.,16 and Mutoh, et al.,14 patients followed for 12 to 89 months and 6 months to 96% at 2 years.23,25,31 Similarly, varied follow-up periods ing allograft compared with those receiving autograft?24 to 87 months. Are fusion rates lower in patients receiv- was noted by Fernyhough, et al., for patients followed for received an allograft without plating. A fusion rate of 59% that fusion actually occurred. Unfortunately phenomena would occur and whether it was at the minim- or maximal end of the range. One can see that fusion rates can not be compared for autograft and allograft, plated and nonplated cases, or one-level and multilevel decom- pression when the standard method is used. Our study clearly revealed the above difficulty. In our example, comparison of fusion for one- and two-level cases was quite different when using the literature method of calculation of fusion rate from when the median time of fusion was used. Our study is limited to patients who underwent cervical corpectomy followed by use of fibular allograft and plating. Comparability of the results to fusion of the lumbar/thoracic region, cases of discectomy, autograft use, and lack of plating would require future trials. The current study also uses a definition that requires presence of any trabeculation as signifying fusion. In the future, more accurate methods of evaluating fusion, such as with the use of computerized tomography, may lead to earlier median times to fusion than those reported here. Last, the median time to fusion is limited by the fact that the date the x-ray film was obtained determines the date of the event for the Kaplan–Meier method of estimation. Unfortunately determining the precise date of fusion would require continuous imaging, which would be impractical; however, this limitation is evident in all studies reported in the literature. Despite these restrictions this study was paramount in illustrating the importance of representing fusion rate as a time-dependent phenomenon, based on the use of the Kaplan–Meier method of estimation.

Conclusions

Fusion rate is a time-to-event phenomenon and is more accurately represented using the Kaplan–Meier method of estimation.

References

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