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# Efficacy and outcome of autologous transplantation in rare myelomas

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## ABSTRACT

### Background

As the rare myelomas; IgD, IgE, IgM and non secretory only compose a small proportion of any studies, there is relatively little known about their progress in the era of peripheral stem cell transplantation.

### Design and Method

We have used the European Group for Blood and Marrow Transplantation Myeloma Database to compare the outcome following autologous transplantation of over 20,000 common myelomas (IgG, IgA and light chain myeloma) with the outcome in rare myelomas; 379 IgD, 13 IgE, 72 IgM and 976 non-secretory.

### Results

The study confirms the multiple adverse prognostic factors seen in IgD myeloma. Somewhat surprisingly, IgD and non secretory myeloma patients both had higher complete remission rates before and after transplantation than common myelomas. However while the overall survival of non secretory myeloma was similar to that of the common myelomas, survival in IgD myeloma was significantly worse (although better than reported survivals in non transplanted patients); this is due to higher transplant related mortality and relapse/progression rate. The survival in IgE and IgM myeloma following transplantation appears to be very poor.

### Conclusions

This report provides data on the biological features of the rare myelomas. The overall survival of IgD, IgE and IgM myeloma is poor following auto-transplantation but substantially better than reported survival in non-transplant patients.

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## INTRODUCTION

More than 90% of myelomas will have IgG, IgA or Bence Jones Protein only ideotypes. IgD and non-secretory (NS) myelomas are uncommon while IgM and IgE myelomas are rare or extremely rare.[1] Survival in IgD myeloma is generally accepted to be poorer than for *common* myelomas.[2,3,4,5] The situation for non-secretory myeloma is less clear; originally thought to confer an adverse prognosis the majority of authorities now suggest that the prognosis is similar[6,7,8] to or possibly better[9,10] than *common* myeloma. It should be noted that these results are based only on a small numbers of cases in the series reported. It would also seem that survival with standard therapy in IgE and IgM myeloma may be somewhat less than the common myelomas.

Little is known about the impact of conventional transplant strategies on the outcome of any of the rare myelomas. The introduction of alternative strategies for allogeneic transplantation with low intensity conditioning, inclusion of new drugs in autologous approaches and new non transplant therapeutic modalities may improve the outlook for all myeloma patients. It is thus an opportune time to review the outcome of conventional transplantation strategies on the rare myelomas when compared with a group of common myelomas. In this study we have used the myeloma database of the European Group For Blood and Marrow Transplantation (EBMT) to study the outcome of autologous transplantation in IgD, IgE, IgM and NS myeloma and have compared the outcome with that of over 20,000 common myelomas.

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## DESIGN AND METHODS

A retrospective study was carried out of 22244 patients with multiple myeloma who underwent autologous transplantation between 1986 and 2007 with complete data for age, sex and type of myeloma. Half of the patients were transplanted after the year 2000. The numbers of patients with each type of myeloma are shown in Table 1. Patients with IgG, IgA and Bence-Jones (BJ) myeloma were collectively described as 'common myeloma'. Patients with plasma cell leukaemia were analysed in a concurrent analysis.[11] Solitary plasmacytoma and amyloidosis were also excluded. All patients were reported to the EBMT registry using MED-A (limited data set) or MED-B (more extensive data set) forms. All 22444 autografted patients were included in the study, regardless of availability of complete MED-A or MED-B data. The number of patients that could be evaluated for each parameter was noted and the proportion of evaluable patients is included in the results. Factors known to affect the transplant outcome from previous EBMT studies[12] were also analysed.

### Statistical methods

Groups were compared using the $c^2$ test for frequencies and the Mann Whitney test for continuous variables. Survival curves were generated according to the Kaplan Meier method and differences were tested with the log-rank test. Cumulative incidence curves were produced using the proper non-parametric estimator, and the Gray test was used for comparisons. Adjusted effects on overall survival (OS), progression free survival (PFS), relapse incidence (REL) and non relapse mortality (NRM) were estimated in terms of hazard ratios (HR) by Cox models. Adjusted effects on Response were estimated in terms of odds ratios (OR) by logistic

regression; the constant term represents the baseline odds ratio, that is the ratio between probability of response and probability of no response for a patient with all covariates equal to zero. The multivariable models considered as adjustment factors age, gender, stage at diagnosis, use of total body irradiation (TBI), interval from diagnosis to transplant and except for non-secretory patients light chain type. 16956 (76%) cases with complete patterns of covariates were included: 15959 common myelomas, 215 IgD, 47 IgM and 735 NS (proportions similar to the whole of the group). IgE was excluded on the account of the small number of cases. Relevant selection bias is unlikely as all characteristics, PFS and OS appeared very similar in the select group and the 'missing' group. For the interpretation of Table 3, if the 95% CI for HR or OR includes the value 1 the effect of the factor is non-significant at the 5% level; while intervals all above or all below 1 indicate respectively significant risk/protective factors. The size of the effect is proportional to deviation from 1. All analyses were carried out using the SPSS statistical software (version 12.0.1) except the analyses of cumulative incidence curves, which were carried out using the package CMPRSK in R 2.4.1.

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## RESULTS

*Characteristics of the myeloma subgroups*

The patient characteristics at diagnosis are shown in Table 1, with percentage availability of results for each variable shown. In most statistical comparisons the IgE/IgM group have been omitted to avoid invalidating the analyses. Comparison with common myelomas shows a statistically significant excess of male patients with IgD, IgE and IgM myeloma, more advanced Salmon Durie stage, and a greater degree of bone involvement. In IgD myeloma the $\kappa$:$\lambda$ ratio is reversed (p=0.001). It can also be seen that more patients with IgE myeloma also had an excess of $\lambda$ light chains but IgM myeloma has the usual ratio of $\kappa$/$\lambda$. NS myeloma also had a higher percentage of patients with Stage III myeloma at diagnosis (p<0.001) which may be at least in part related to a significant increase in patients with major bone abnormalities at diagnosis (p<0.001) and the difficulty in diagnosing this form of myeloma due to the absence of a typical 'spike' on protein electrophoresis.

Reviewing the discreet variables it can be seen that IgD myelomas are marginally younger, have a lower M protein level and higher albumin than common myelomas whereas these patients presented with significantly lower haemoglobins, higher $\beta_2$ microglobulins and had higher serum creatinine (all comparisons, p<0.0001). While NS myeloma patients were also significantly younger than the common myeloma patients, with significantly higher albumin and haemoglobin levels the serum creatinine was significantly lower (all comparisons, p=0.0001). The IgM patients showed the highest calcium levels with the lowest haemoglobins but $\beta_2$M, albumin and creatinine did not differ greatly from the common myelomas. The time from diagnosis to transplantation was similar for common, IgE/IgM and NS myeloma while

IgD myelomas had a median time to transplant approximately three weeks shorter. It should be noted while the p values for all these differences are highly statistically significant, on account of the number of patients analysed, not all are of biological significance. Furthermore, the numbers of IgE patients in which some of the data are reported is too low to allow any conclusions to be drawn. The median time to transplant suggest most patients were transplanted as part of their first line therapy but this is not specified.

*Transplant related variables*

Table 2 shows the transplant related variables including graft type, use of TBI and conditioning regimens. While the differences in the use of stem cells other than PBSC are small the IgE and IgM group have a small increase in the proportion of bone marrow cells used. It can be seen that IgD myelomas had a greater use of TBI whether alone or in conjunction with Melphalan whereas both IgM and NS myeloma were less likely to receive TBI; there were also some differences in the regimes used to treat non secretory myeloma compared to common myeloma.

*Transplant outcomes*

Comparison of performance status and disease response to induction therapy in patients undergoing transplantation is shown in Table 2. Again percentage availability for each variable is shown where appropriate. There was no difference in the post transplant recovery between IgD, IgE/IgM, non secretory and common myelomas. Disease response in NS myeloma was as defined by the reporting institutions. Kaplan Meier plots of OS and PFS, REL and NRM are shown in Figures 1a-d respectively.

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*IgD myeloma*

IgD myelomas appeared to have a better response to therapy than common myelomas with a greater proportion of patients being transplanted in complete remission (CR), this however did not give rise to a difference in performance status. Similarly a greater proportion of IgD myeloma patients achieved CR post transplant. There was no difference in engraftment rates or the time to neutrophil and platelet recovery post transplantation.

While the median survival of the common myeloma is 62.3 months (Figure 1a) (Confidence Intervals shown in Table 2) the OS of IgD patients is significantly lower being 43.5 months ($P$=0.0001) despite the high CR ratio and presumably related to the high relapse rate (Fig 1c $P$=0.0004). Median PFS is 27.4 and 23.7 months respectively ($P$=0.017) (Figure 1b, confidence limits in Table 2). Although subject to cautious interpretation a plateau like flattening of the graph is seen not only for common myeloma but also IgD myeloma.

*IgM myeloma*

Although the proportion of patients with IgM achieving CR prior to transplant was the lowest of all the groups, the transplant appears to have a beneficial effect with the numbers achieving CR rising to 34% with a similar improvement in the proportion of partial remissions (PR). Engraftment appears to be satisfactory in this group. OS and PFS are markedly similar to IgD myeloma (Figures 1a and 1b) but the small number of patients results in wider confidence limits, shown in Table 2.

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*IgE myeloma*

Although the numbers of the patients in this group are so small as to make any conclusion tentative, this group achieved the highest level of CR prior to transplant. Despite this median OS was the worst of all groups even though PFS was similar or better than IgG and IgM myeloma. There did not appear to be any difficulty with engraftment but NRM for IgM and IgE was the highest of all types (Figure 1d) although not statistically significant.

*Non secretory myeloma*

Table 2 shows NS myelomas had higher CR and CR+PR rate than common myelomas at mobilisation and conditioning although this did not result in a difference in performance status at transplantation. The higher CR and CR+PR rate is presumed to contribute to the higher response rates post transplant; with CR rates of 48.8% observed, the highest excluding the small IgE group. There is no overall difference in engraftment data. Figure 1a and 1b confirm the superior O.S. (64.6) and PFS (33.6 mo) of NS myeloma (C.I. shown Table 2); PFS is statistically significantly superior to the common myelomas ($P$=0.0002) however this is not reflected in a statistically superior OS.

*Subsequent transplantation*

Table 2 also shows the number and relative percentages of patients with each type of myeloma proceeding to a further transplant and the median time to second transplant (irrespective of type). It would appear patients with common myelomas were more likely to receive a second transplant and IgD myeloma least likely however the differences are small and unlikely to affect the overall survival data.

Curiously in IgE/IgM myelomas the median time to second transplant appears longer. On account of the observational nature of this part of the study the data are not appropriate for further statistical analyses.

*Adjusted analysis of response*

Data from this analysis is summarised in Table 3. 'Light chain type' has been excluded from the analysis shown in the table but was included in a companion analysis which showed little change in most parameters. IgD has a significantly adverse HR for OS, PFS and relapse. When light chain type is included (data not shown) the HR is reduced and looses it significance suggesting the adverse prognosis is related to the much greater incidence of λ light chain in IgD myeloma, demonstrated in Table 2.

The last two columns of Table 3 confirm that patients with IgD and NS myeloma have a significantly greater prospect of achieving CR than the control group which is not stage dependent. TBI usage and age are unfavourable factors while female gender is favourable. When the light chain is included, (data not shown) the λ chain somewhat surprisingly is a favorable factor. It can be deduced that this may be related to the high proportion of λ chain IgD myeloma achieving a good response but with poor overall survival due to the high relapse rate in this group. However, when CR+PR is reviewed there is no difference between IgD, IgM, NS and control myelomas in achieving at least a PR. Stage III becomes an adverse factor but the effect of chain isotype is lost. There are significant differences in the HR for age, gender, TBI and time to transplant but in general these retain their impact on the model. In producing this model it was noted that the use of TBI overlapped completely with the year of transplant allowing analysis of only one or other of those variables.

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## DISCUSSION

Autologous transplantation with stem cells from bone marrow or peripheral blood has been used to treat myeloma for over two decades; the ability of cytokines to mobilise stem cells in the peripheral blood has led to a huge rise in the use of this mode of treatment.[13] Initial impressions of benefit shown in a single centre non randomized series[14] have now been confirmed in multicentre prospective randomised clinical trials.[15,16] However, the numbers of rare myelomas such as IgD, IgE and IgM in any such trial are usually insufficient to allow any conclusion regarding outcome to be drawn while non-secretory myelomas are often excluded from clinical trials because of the difficulty in assessing response in this condition. We have therefore used the EBMT myeloma database containing over 22,000 patients to obtain information on the outcome of transplantation in these rare conditions and factors affecting these outcomes.

The overall thrust of this study is to show that the rare myelomas IgD, IgE and IgM have a worse prognosis than the common myelomas. In contrast non-secretory myelomas should be considered together with the common myelomas–although there is a better progression free survival the (possibly related to the lack of the usual conventional markers of disease progression in myeloma) overall survival is only marginally better than that of the common myelomas. On reviewing the data in more detail, our study confirms that IgD myeloma has a significantly worse prognosis associated with adverse prognostic factors in keeping with previous series describing this condition.[17] This may be related to the high proportion of patients with raised proliferation rates combined with abnormal gene expression profiles demonstrated in a small group (n=12) of patients with IgD myeloma.[18] As with common myelomas

there is a small tail of long survivors confirming the few case reports of long survival in this condition[19,20,21] and also IgE myeloma.[22] Of note, patients with IgD myeloma received TBI in greater numbers than with the common myelomas and all of the other rare myelomas and whilst this is associated with a poorer outcome,[13] it is not sufficient to account for the 19 month difference in overall survival of all patients with IgD myeloma. In fact patients with IgD had higher rates of complete remission both before and after transplantation, but unfortunately this did not translate into a better overall survival due to the very high relapse rate.

In contrast, the NS myelomas are seen to have both favourable and adverse prognostic factors.[23] These patients appear to achieve a very high level of CR both before and after transplantation possibly because of the lack of identifiable paraprotein. Progression free survival appears superior to common myelomas ($P$=0.0003) but there is no difference in overall survival between the two groups. NS myeloma treated conventionally has been reported as having survival similar to common myeloma.[1,24] In a single institution study of transplanted patients NS myeloma had a significantly better outcome than all other myeloma types although there are only 6 NS patients in the series.[25] The current much larger study suggests that NS myeloma behaves similarly to common myelomas and should be treated similarly.

This retrospective analysis of the 'rare' myelomas has resulted in the production of the largest reported database of rare myelomas to date. Inevitably with the statistical power obtained by large numbers there is the down side of poor reporting of certain parameters and the fact that while differences may be shown to be statistically significant, their biological significance may be of doubtful importance. Furthermore, while data such as overall survival and progression free survival are robust, it is

necessary to recall that only the younger and fittest patients will make it through to transplantation. Whilst there is a suggestion from our data that both IgD and NS myeloma may affect younger individuals, only 25% of myelomas may come to transplant, as of all possible cases of myeloma, roughly 50% are over the age of 68 and co-morbid disease may result in up to 50% of those under that age not undergoing transplantation.[26]

It has recently been suggested that a very high incidence of the translocation t(11:14) (q13:q32) is the hallmark of NS, IgE and IgM myelomas (but not IgD)[27] while Feyler *et* al., have suggested that IgM is characterised by a CD20-, CD56-, CD117- immunophenotype in addition to the t(11;14).[28] This translocation in NS patients may relate to the significant improvement in the progression free survival but is not translated into superior overall survival. In contrast the survival for IgM and IgE myelomas is very similar to that of IgD myeloma although the small size of these groups means that the differences are not of statistical significance. Of note there is no information on survival in the Avet-Loiseau report.

The multivariate study confirms that NS myeloma would appear to be a disease of younger patients in keeping with the other reports of relatively young median age[9,7] - with a 3:2 male predominance. Despite the younger age NS patients present with advanced disease and more bone lesions than common myeloma (and even IgD myeloma). In contrast, they have significantly better median haemoglobin, albumin and creatinine at presentation than common myelomas inferring that the major effect of NS myeloma is on the skeletal system rather than the other organs. $\beta$2 microglobulin levels were similar to common myelomas. The difficulty in defining the level of response in NS myeloma has not been resolved in this study as we have used the reporting institutes assessment; in years to come the serum free light chain

analysis[29,30] and flow cytometry[31] will bring some objectivity to this difficult assessment.

Our study provides robust confirmation of the inversion of the κ:λ light chain ratio in IgD myeloma with three-quarters of patients having λ light chains. The data for IgE myeloma shows some similarity but IgM myeloma has a similar κ:λ ratio to the common myelomas. For IgD myeloma this would appear to be another adverse prognostic factor to accompany a significantly greater number of bone lesions and a greater proportion of stage III disease. A lower haemoglobin and higher $\beta_2$ microglobulin and creatinine are also associated with poor prognosis. Due to the poorer reporting of this data in IgE myeloma no comment can be made about this group. Although we show that rare myelomas frequently have more adverse prognostic factors than the common myelomas and despite a higher CR ratio that this is reflected in a poor median survival following transplantation, it should be noted that the survivals are significantly better, often more than double that in the best historical series, although these series represent the outcomes of conventional therapy in patients of all ages.[17] Two recent publications also suggest a poor prognosis for patients with IgM myeloma.[28.32] Figure 1c shows the relapse incidence in IgD to be significantly higher but associated specifically with the high incidence of λ chain in this isotype (Table 1), while the non-relapse mortality incidence of IgE and IgM myeloma looks much higher than the other myelomas (Figure 1d).

In conclusion the study suggests that patients with IgD, IgE and IgM myelomas appear to present with adverse prognostic factors and have survival worse than the common myelomas and NS myeloma following transplantation. Nevertheless, survival of transplanted patients in these rare myelomas is much better than anything previously recorded indicating that

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transplantation should not be abandoned as a therapeutic modality. It remains to be seen what the new drugs such as Thalidomide, Lenalidomide and Bortezomib can do for these conditions.

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## Authorship and Disclosures

CM and JA designed the study; AvB produced the files for statistical analysis; SI performed the statistical analysis; CM, MD and GG wrote the paper. All authors reviewed and agreed the final paper. The authors declare neither conflict of interest nor competing financial interests.

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**Table 1.** Patients characteristics of the common types, NS Myeloma, IgD, IgM & IgE, (n=22244).

| **Patients characteristics** | | Usual Myeloma IgG n=12245 (55%) IgA n=4533 (20%) BJM n=4026 (18%) | Data Available % | IgD n=379 (1,7%) | Data Available % | IgE n=13 (0,1%) | Data Available % | IgM n=72 (0,3%) | Data Available % | Non Secretory n=976 (4,4%) | Data Available % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gender %* | Male | 58.2* | 100 | 64.9* | 100 | 76.9 | 100 | 62.5 | 100 | 56.2* | 100 |
| Age†† | Yrs | 55.6 | 100 | 54.3 | 100 | 54.6 | 100 | 56.2 | 100 | 54.4 | 100 |
| Albumin† | g/l | 37.0 | 15.4 | 40.5 | 12.7 | 41 | 7.7 | 35 | 12.5 | 40.0 | 12.7 |
| Calcium† | mmol/l | 2.38 | 28.4 | 2.48 | 23.0 | 2.3 | 15.4 | 2.75 | 15.2 | 2.42 | 17.1 |
| Creatinine† | mmol/l | 92.0 | 26.5 | 130.5 | 23.7 | 65 | 15.4 | 85 | 15.2 | 80.0 | 16.6 |
| Haemoglobin† | g/dl | 11.0 | 31.7 | 10.1 | 25.9 | 11.8 | 23.1 | 9.35 | 19.4 | 12.1 | (23.0) |
| $B_2M$† | mg/l | 3.1 | 21.8 | 4.4 | 20.6 | 5.4 | 15.4 | 3.3 | 15.2 | 2.6 | (18.6) |
| Time to Tx† | months | 7.7 | 100 | 6.9 | 100 | 6.9 | 100 | 7.6 | 100 | 7.6 | (100) |
| Stage (at ** diagnosis Salmon Durie) | I | 13.2 | | 6.4 | | 10 | | 6.3 | | 6.9 | |
| | II | 20.5 | 80.7 | 16.8 | 75.2 | 40 | 76 | 19.0 | 87 | 18.0 | 79.0 |
| | III | 66.3 | | 76.8 | | 50 | | 74.6 | | 75.1 | |
| Bone ** (structure at diagnosis) | Normal | 23.8 | | 17.3 | | 25 | | 12.8 | | 7.1 | |
| Light Chain Type** | κ | 65.5 | 100 | 24.7 | 75.7 | 40 | 76 | 70.9 | 76 | | N/A |
| | λ | 34.5 | | 75.3 | | 60 | | 29.1 | | | N/A |
| Graft Source** | PBSC | 96.9 | | 96.2 | | 84.6 | | 95.7 | | 95.7 | |
| | BM | 2.0 | 98.4 | 3.5 | 98.4 | 15.4 | | 4.3 | | 3.1 | |
| | BM and PBSC | 1.1 | | 0.3 | | 0 | 100 | 7.0 | 97.2 | 1.2 | 98.4 |
| Use of TBI†† | No | 92.2 | | 86.5 | | 84.6 | | 98.5 | | 94.5 | |
| | Yes | 7.8 | 94.2 | 13.5 | 93.7 | 15.4 | 100 | 1.5 | 97.7 | 5.5 | 94.7 |
| Conditioning for TX†† | Mel | 75.7 | 46.9 | 64.8 | 44.3 | 60.0 | | 87.5 | | 73.6 | |
| | Other | 24.3 | | 35.2 | | 20.0 | | 12.4 | | 26.4 | |

** p <0.018 for IgD/NS as a discreet variable, ** p<0.001 for IgD/NS discret variables, † p<0.001 for IgD/NS continuous variables, †† p<0.0001 for IgD/NS myeloma.*

**Table 2.** Comparison of disease response to therapy and engraftment in IgD, IgE, IgM and NS myelomas with common types.

| Characteristic | | Common Myelomas | | IgD | | IgE | | IgM | | NS Myeloma | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | % | % Available | Data | % Available | Data | Info Available | Data | Info Available | Data | % Available |
| Disease Response at Conditioning | CR** | 11.9 | 94.7 | 20.1 | 95.8 | 33.3 | 92.3 | 7.8 | 88.9 | 28.9 | 91.0% |
| | PR | 69.0 | | 65.8 | | 58.3 | | 68.8 | | 53.9 | |
| | No Response | 12.3 | | 8.0 | | 8.3 | | 17.2 | | 10.4 | |
| | Rel/Prog untreated and other | 6.8 | | 6.1 | | 0.0 | | 6.3 | | 6.8 | |
| | | | | | | | | | | | |
| Performance Status at Transplant | Good | 93.8 | 64.7 | 93.7 | 59.1 | 100.0 | 76.9 | 94.9 | 81.9 | 93.7 | 72.8% |
| | Poor | 6.2 | | 6.3 | | 0.0 | | 5.1 | | 86.3 | |
| | | | | | | | | | | | |
| Disease Response post transplant | CR**<br>CR or PR* | 28.2<br>61.8 | 89.5 | 43.8<br>66.0 | 88.8 | 60<br>70 | 76.9 | 33.9<br>53.2 | 86.1 | 48.8<br>66.3 | 84.6 |
| Engraftment | Engrafted<br>Not engrafted<br>Dead without engrafted | 97.6<br>1.8<br>0.6 | 97.3 | 97.5<br>1.7<br>0.8 | 96.0 | 100<br>0<br>0 | 92.3 | 98.5<br>0<br>1.5 | | 98.2<br>1.3<br>0.5 | 98.0 |
| Median† Survival | Months<br>Confidence Interval | 62.3<br>60.5 – 64.1 | | 43.5<br>36.1-50.9 | | 33.4<br>20.1-46.8 | | 44.7<br>33.8–55.6 | | 64.6<br>57.3-71.8 | |
| Median Progression free Survival†† | Months<br>Confidence Interval | 27.4<br>26.7–28.0 | | 23.7<br>20.4-26.9 | | 27.8<br>19.9-35.8 | | 22.8<br>19.3-26.4 | | 33.6<br>29.4-37.8 | |
| Second SCT | Auto<br>N=7223 | 6838<br>(32.9%) | | 4<br>(30.8%) | | 23<br>(31.9%) | | 90<br>(23.7%) | | 268<br>(27.4%) | |
| | Allo<br>N=1254 | 1180<br>(5.7%) | | 1<br>(7.7%) | | 3<br>(4.2%) | | 20<br>(5.3%) | | 50<br>(5.1%) | |
| | Median time to 2nd transplant (days) | 128 | | 143 | | 208 | | 112 | | 132 | |

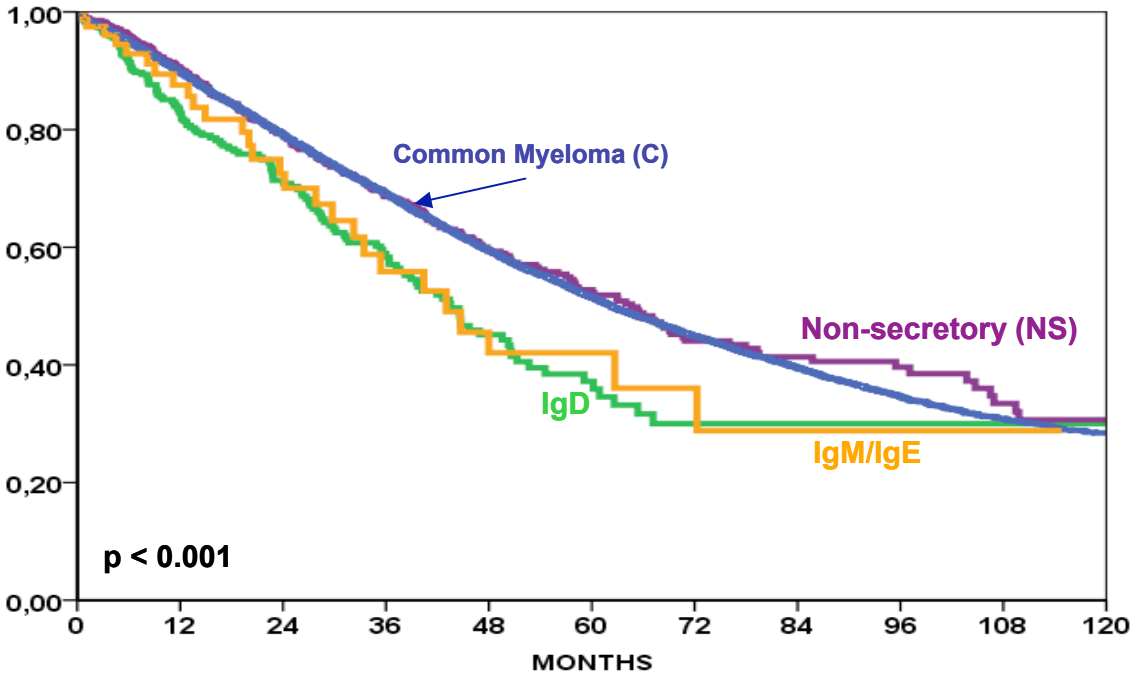
** p=0.018; ** p=0.001; † p=0.0003 for IgD/NS; †† p=0.0001 for IgD/NS.*

**Table 3.** Multivariate Analysis on risk factors for outcome.

| | Overall survival | Progression Free Survival | Relapse | Non Relapse Mortality | CR *vs.*<CR | CR + PR *vs.*<PR |
|---|---|---|---|---|---|---|
| IgD vs. common | **1.03-1.68** | **1.01-1.49** | **1.04-1.56** | 0.55-1.70 | 1.49-2.65 | 0.95-1.76 |
| IgM vs. common | 0.85-2.43 | 0.63-1.59 | 0.44-1.36 | **1.08-5.39** | 0.65-2.57 | 0.42-1.54 |
| Non Secretory vs. common | 0.82-1.1 | **0.71-0.91** | **0.70-0.90** | 0.63-1.17 | **2.35-3.25** | 1.03-1.46 |
| Age (+1 year) | **1.01-1.22** | **1.01-1.02** | **1.008-1.012** | **1.006-1.021** | **0.98-0.99** | **0.98-0.99** |
| Gender (F vs M) | **0.86-0.97** | **0.84-0.92** | **0.83-0.91** | NS | **1.07-1.23** | 1.00-1.14 |
| Stage II vs. I | **1.06-1.33** | **0.13-1.21** | **1.02-1.21** | 0.91-1.43 | 0.96-1.24 | 0.93-1.18 |
| Stage III vs. I | **1.47-1.79** | **1.28-1.48** | **1.25-1.45** | **1.30-1.92** | 0.84-1.06 | **0.79-0.97** |
| TBI | **1.16-1.37** | **1.03-1.18** | NS | **1.18-1.66** | **1.01-1.31** | **1.36-1.78** |
| Diagnosis to tTransplant (+ 1 month) | **1.002-1.004** | **1.001-1.003** | **1.001-1.003** | **1.002-1.006** | **0.995-0.999** | **0.997-0.999** |

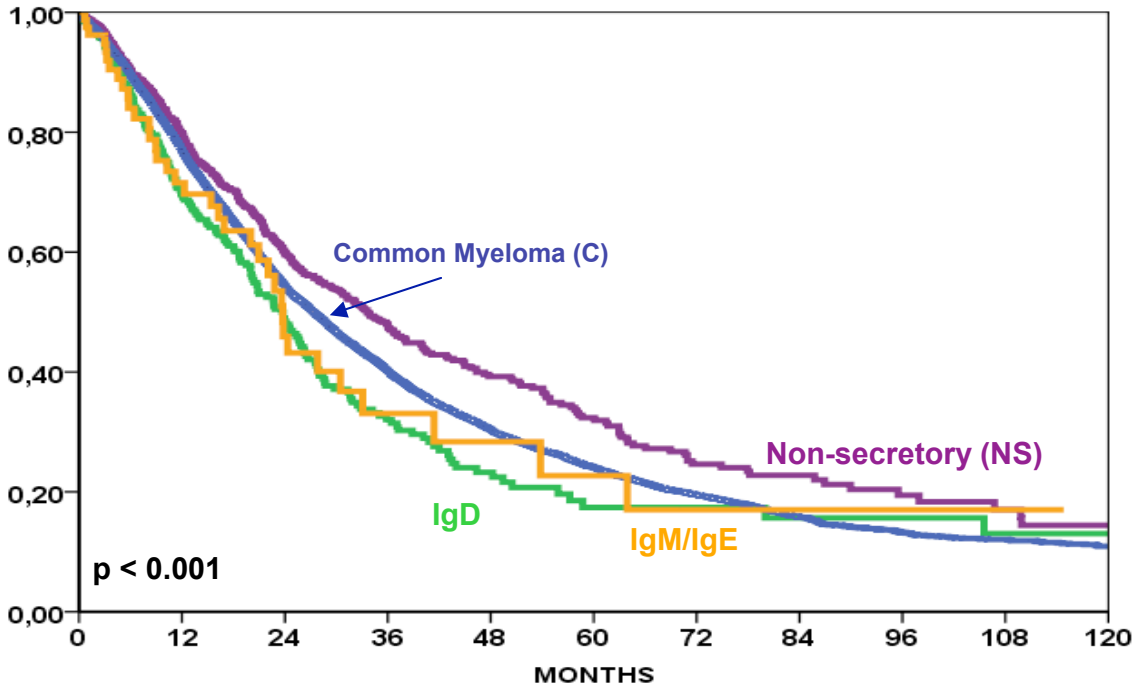
*Results shown are 95% confidence limits for odds ratio – results which do not bracket 1 are statistically significant. Thus for IgD v control IgD is at significantly greater risk of OS, PFS and relapse but not NRM despite the fact the rate of CR is significantly higher than common (but not CR + PR). NS indicates not included in analysis as not significant in the univariate analysis.*

**Figure 1a**




| | | | | | |
|---|---|---|---|---|---|
| IgD (379) | 208 | 140 | 94 | 28 | 12 |
| IgM/IgE ( 85) | 47 | 30 | 18 | 8 | 2 |
| NS (976) | 585 | 394 | 364 | 115 | 39 |
| C (20,804) | 13,158 | 8,903 | 6,116 | 2,718 | 669 |

**Figure 1b**




| | | | | | |
|---|---|---|---|---|---|
| IgD (379) | 208 | 140 | 94 | 28 | 12 |
| IgM/IgE (85) | 47 | 30 | 18 | 8 | 2 |
| NS (976) | 585 | 394 | 364 | 115 | 39 |
| C (20,804) | 13,158 | 8,903 | 6,116 | 2,718 | 669 |

**Figure 1c**

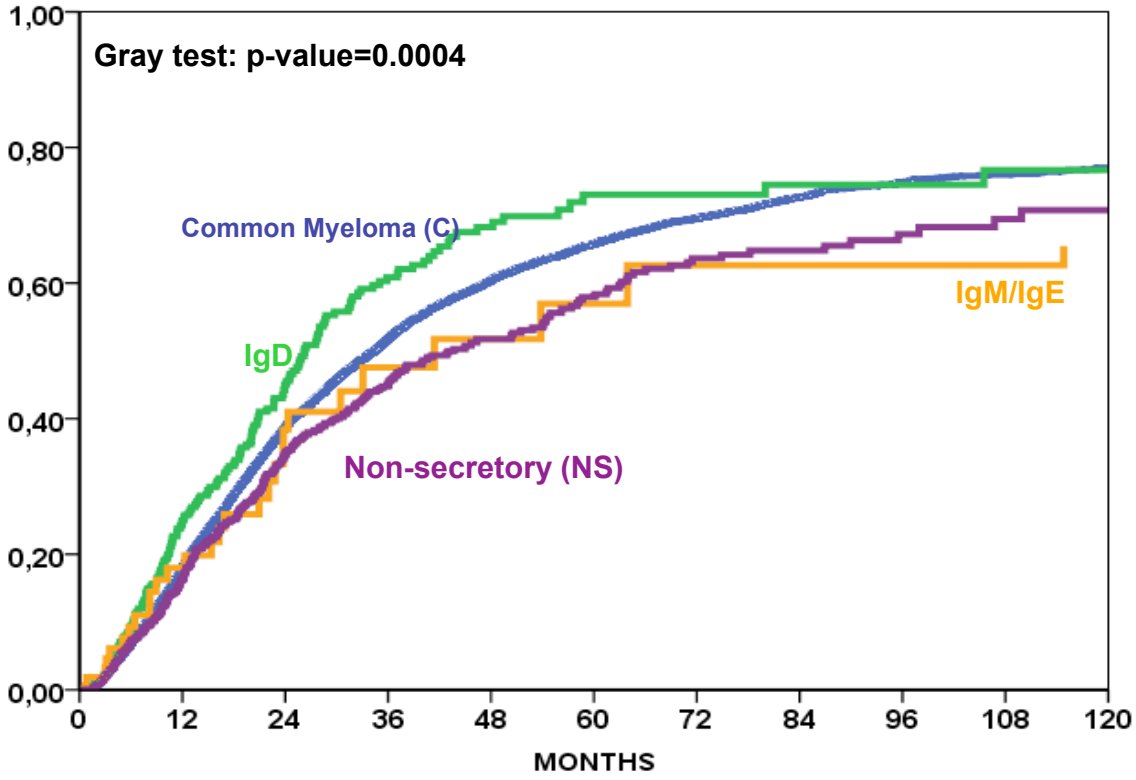

Gray test: p-value=0.0004
1,00
0,80
0,60
0,40
0,20
0,00
0
12
24
36
48
60
72
84
96
108
120
MONTHS
Common Myeloma (C)
IgD
IgM/IgE
Non-secretory (NS)

**Figure 1d**

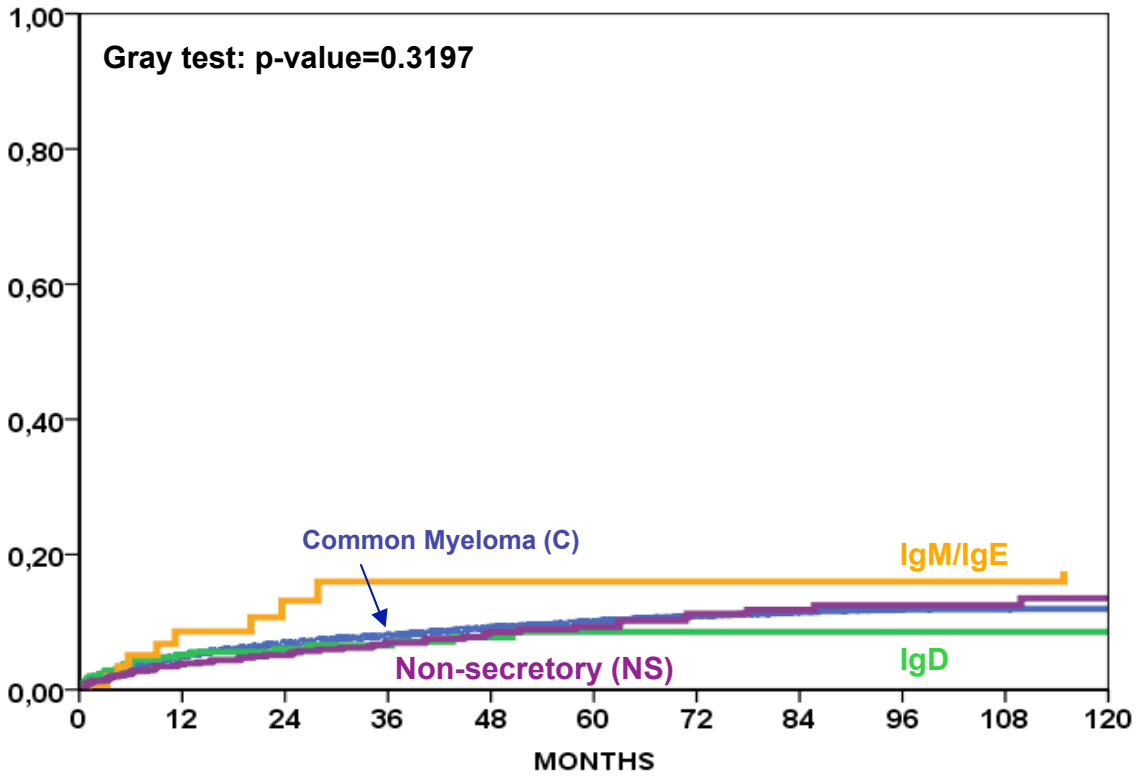



**Figure 1. a.** Overall survival of rare myeloma. **b.** Progression-free survival of rare myeloma. **c.** Relapse incidence of rare myeloma. **d.** Non-relapse mortality of rare myeloma.