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Rapidly changing myeloma epidemiology in the general population: increased incidence, older patients, and longer survival

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Abstract

The incidence of multiple myeloma is characterized by a steep increase with advancing age. Dramatic improvements in survival have been reported in clinical trials; however, elderly patients are generally underrepresented in these. The aims of this study are to review patterns of incidence and survival in multiple myeloma in the general population. We searched PubMed for population-based studies on trends in incidence and survival published between January 1, 2000 and June 30, 2017 and based on regional or national cancer registries and report the following results of the review.

The age-adjusted incidence of multiple myeloma has increased during the second half of the 20th Century in some countries but remained stable in areas with high case ascertainment and access to universal medical care. The crude incidence is increasing globally due to an ageing population. Survival rates have improved and 5-year relative survival rates are now around 50% and over 60% in patients 65–70 years or younger.

Preliminary data suggest a 3-fold increase in the prevalence of multiple myeloma.

We conclude that the number of multiple myeloma patients is increasing in the general population due to (1) aging populations and (2) more patients living longer due to modern drugs.

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Authorship contribution.
All authors were involved in designing the study, IT performed the systematic review. IT and OL wrote the paper. All authors assisted with the manuscript preparation.

Keywords

multiple myeloma; incidence; prevalence; overall survival; trends

Introduction

Multiple myeloma, a malignant plasma cell disorder, has the second highest incidence among haematological malignancies and it constitutes about 15% of annually reported cases of haematological malignancies in the Western world (1). Because the average age of onset is 70–75 years, multiple myeloma is mainly a disease of the elderly and it has a steep increase in incidence with advancing age (2–3). The incidence of multiple myeloma is about 1.5 times higher in males than in females (4). Specifically, in the U.S., the 2011–2012 incidence of multiple myeloma (adjusted to the US standard population) was 7.8 per 100,000 person-years and 5.1 per 100,000 person-years for males and females, respectively (5). The corresponding numbers were 7.9 per 100,000 person-years and 5.5 per 100,000 person-years for the estimated 2015 incidence of multiple myeloma in Sweden (6). Furthermore, in the U.S. population, the incidence is 2- to 3-fold higher in African-Americans compared to whites; and Asians have lower incidence than whites (7).

Currently, there is not yet an established curative treatment available for patients diagnosed with multiple myeloma. However, in the past 10–20 years the introduction of modern therapies has resulted in deep and durable treatment responses in large proportions of patients, which in turn have resulted in long-term disease control and also giving hope of a cure in the future (8). Clinical outcomes improved with the introduction of high-dose melphalan with autologous stem cell support (HDM-ASCT) which was developed in the 1980s and 1990s (9–10) and was followed by a range of modern drugs which started around the turn of the 21st Century. Today, multiple myeloma can be treated with several classes of drugs such as: proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide), cytotoxic drugs (cyclophosphamide and melphalan, as well as other combinations such as DCEP and VTD-PACE), HDAC inhibitors (panobinostat), naked monoclonal antibodies (daratumumab, elotuzumab), and allogeneic transplant. In addition to these classes of drugs, several newer drugs are already far along in clinical development including the development of antibody conjugates, bite antibodies, targeted small molecules, and CAR-T cell therapy.

As part of the approval process for the newer drugs, randomized phase 3 trials have consistently shown improvement and, in particular, when these clinical trials were conducted in countries with limited access to newer drugs (i.e. with limited options to re-treat progressing disease) increased overall survival with many of these newer drugs (11–15). However, due to the nature of eligibility criteria of clinical trials, it is difficult to generalize the results from the studies to all multiple myeloma patients diagnosed in the general population. For example, elderly patients and patients with comorbidities are often excluded from clinical trials and population-based studies are needed to fully evaluate the impact of the new treatment modalities on survival in unselected patients. The aims of this study are to review patterns of incidence and survival in multiple myeloma in the general population.

Methods

We searched PubMed for studies using the search words multiple myeloma and trends in incidence and multiple myeloma and trends in survival with publication date between January 1, 2000 and June 30, 2017 and identified 240 and 305 papers, respectively. We examined abstracts and text to identify papers that were based on regional or national registries, compared changes over a time period of more than 5 years and covered a period reaching year 2000 or later. Eleven studies on trends in incidence and 17 studies on trends in survival fulfilled these criteria.

In a sub-analysis, for comparison, 6 large, non-population-based, single institution studies of survival trends were included.

Results

Incidence trends

Incidence and mortality rates obtained from population registries show a great variation around the world. Several studies have reported a dramatic increase in multiple myeloma incidence and mortality in the second half of the 20th century. In the U.S. there was a 2-fold to 3-fold increase in multiple myeloma mortality from 1950 to 1975. The increase was seen in both races, but was greater in nonwhites than whites and primarily occurred in people over 55 years of age (16). In England and Wales, the age-adjusted mortality increased more than 5-fold from 1950 to 1979 (17). In contrast, two studies from Minnesota, U.S. and Malmö, Sweden found no increase of age-adjusted multiple myeloma incidence from 1945 to 2001 and from 1950 to 2005 respectively (2–3). These studies were based on data from defined populations with a high access to health care and well developed registration systems. They also reported increasing age-specific incidence rates with advancing age including in the very old.

In a more recent study using SEER (NCI Surveillance, Epidemiology and End Results 9 registries Database) data covering the period 1973 to 2005 multiple myeloma, incidence rates in the U.S. rose slightly from the 1970s to the 1990s before flattening in recent years (18). In a later study from the SEER, age-adjusted incidence increased slightly from 5.5 to 6.1 per 100,000 person-years between the calendar periods 1993–1997 and 1998–2002 (19). In Sweden, the age-adjusted multiple myeloma incidence increased during the first decade of reporting (1960–1970) and remained stable thereafter (6, 20). In Great Britain, the age-adjusted annual incidence (European standard) increased by 69% from 1975–2005 to 2005–2009 from 3.2 to 5.4 per 100,000 person-years, reaching the rates in Sweden that were stable during the whole period at approximately 4.7 per 100,000 person-years (21). The largest increase in Great Britain was in the age group 70–79 years.

In Asia, where the incidence of multiple myeloma is lower the increase over time has been more pronounced. In Korea, the age-adjusted incidence (world standard) in the period 1999–2010 was 1.2 per 100,000 person-years with an annual increase of 4.7%. (22). In Taiwan, the age-adjusted incidence increased between calendar periods 1979–88 and 1994–2003 from

0.36 to 1.21 per 100, 000 person-years for all multiple myeloma patients and from 2.07 to 8.59 in those 70–79 years old (23).

As a consequence of better case ascertainment and an ageing population in Europe and the U.S., there have been substantial increases in crude incidence rate and age distribution of the multiple myeloma population. For example, in Malmö, Sweden, the crude annual incidence increased from 1950–59 to 2000–2005 from 3.3 to 6.8 per 100,000 person-years and the proportion of patients aged 80 years or more from 16% to 31% while the age-adjusted incidence remained stable (3). In Sweden, the crude incidence increased from 5.4 per 100,000 person-years in males and 4.0 in females in 1970 to 8.1 and 6.2 in 2014; the proportion of patients 75 years or older increased from 31,6% to 38,9%. The median age at diagnosis is now 71 years and 24% of patients are 80 years or older (4, 6). In the U.S., the number of new multiple myeloma cases per year is estimated to increase from 19,700 per year (period: 2011–2013) to 32,200 per year (period: 2032–2034) due to changes in the demographic profile of the population, the largest increase being in patients aged 64–84 years with a projected increase of 93% and 91% for men and women, respectively (24).

Survival trends

Improvements in multiple myeloma survival in the general population following introduction of newer drugs was first reported over 10 years ago in a large study from Sweden (25). In that study, survival patterns were evaluated for 14,381 multiple myeloma patients diagnosed 1973–2003; specifically, 1-year and 5-year relative survival rates (RSR) were compared in 4 defined calendar periods during the time-window 1973–2003. The study found 1-year and 5-year RSR to increase from 73% to 83% and from 31% to 36%, respectively. When evaluating survival patterns by age, the 1-year RSR improved in all age groups but improvement in 5-and 10-year RSR was restricted to patients 60 years or younger. The study used data from the Swedish Cancer Registry with high completeness (95%) and accuracy (98%) for multiple Myeloma in a validation study (26). In that first study from 2007, there was no detailed information on treatment available (table I). In a subsequent study 5-year relative survival increased further to 41 % in patients diagnosed 2003–2013 (27).

Studies of survival using the SEER database in U.S

The SEER (NCI Surveillance Epidemiology and End Results 9 registries Database) which started to register multiple myeloma patients in 1973 has fostered a number of reports on trends in survival. In a comparison of 2 calendar periods (1990–1992 and 2002–2004), the authors found an increase in 5-year relative survival from 28.8% to 34.7%. However, the improvement was seen mainly in patients younger than 60 years at diagnosis and was modest and not significant in those over 60. There was no information on treatment but the authors speculated that the improvement was mainly an effect of the introduction of HDM-ASCT (28). In another study, a racial disparity in trends of survival was noted in patients from the SEER database diagnosed 1973–2005. Five-year relative survival increased during 3 calendar periods from 26.3% to 30.8% and 35.0% in whites but there was no significant change in blacks (31.0%, 33.0%, and 34.1%) (18).

In an update of SEER data 1973–2007 5- and 10-year relative survival increased further from 32.8% and 15% in the period 1998–2002 to 40.3% and 20.8% respectively in 2003–2007. The greatest improvement was seen in younger patients but the10-year relative survival now increased significantly also in patients 75 years or older from 6.4% to 8.4%. (29). In an analysis of SEER data, covering 4 calendar periods from 1973 to 2009 and 4 age cohorts, 5-year myeloma-specific survival increased in all age groups. The improvement was most evident in the younger age groups reaching 58 % in the age cohort 51–65 years and decreased with advancing age with no improvement in patients aged 80 years or more (30). Since myeloma-specific survival, which depends on the accuracy of death certificates, was used it is difficult to compare with other studies.

In a study using data from 11 population-based cancer registries in Germany and SEER in U.S. comparing two calendar periods (2002–2004 and 2008–2010) 5-year relative survival increased from 47.3% to 53.8% (Germany) and from 39.8% to 53.2% (U.S.) Survival increased in all age groups but was less pronounced with advancing age. In Germany patients aged 15–44 and 45–54 years 10-year relative survival reached 65% and 41% respectively in the last calendar period. Notably in this study, patients 75 years or older were excluded due to a high proportion in this group notified by death certificate only and there was no information on treatment (31).

The most recent study using SEER data compared 4 calendar periods from 1993 to 2012. In that study, information on treatment of individual patients was not available but the calendar periods were chosen to represent the pre-thalidomide era, introduction of thalidomide, introduction of bortezomib, and early availability of carfilzomib and pomalidomide, respectively. Five-year relative survival increased in all age groups but the improvement was less pronounced in those >75 years and in this group there was no significant improvement in 10-year relative survival. Five-year relative survival in the last calendar period was 61.8% for patients <65 years, 48.5% for those 65–74 years old and 34% for those > 75 years (19).

Population-based studies of survival in Europe and Asia

The EUROCARE-5 database that includes 30 cancer registries in Europe was used in a study comparing trends in survival of hematological malignancies over four calendar periods from 1997–2008. Five-year relative survival in multiple myeloma increased from 29.8% in patients diagnosed 1997–1999 to 39.6% in 2006–2008. The improvement was more pronounced in younger patients and was not significant in patients 75 years or older (32).

Studies from some national or regional cancer registries in Europe have reported higher trends. Five-year relative survival increased from 39.9% in patients diagnosed 2002–2004 to 47.9% in 2008–2010 in a study from 11 population-based cancer registries in Germany (33). Five-year relative survival increased from 45.7% to 49.9% to 55.7% for patients diagnosed in the calendar periods 1988–1996, 1997–2005 and 2006–2009, respectively in a study from the Modena Cancer Registry in Italy (34). There was no significant improvement in patients 75 years or older.

In a populations-based study from Malmö, Sweden, median OS increased in patients 65 years or younger from 24.3 months for those diagnosed 1960–69 to 56.3 months in those

diagnosed 2000–2005 while there was no significant change in those older than 65 years (21.9 vs 26.7 months). Detailed information on treatment of individual patients was available and the authors concluded that introduction of HDM-ASCT was the most likely explanation for the improved survival in the younger patients (35).

In a study from the Swedish Multiple Myeloma Registry 5-year relative survival increased from 47.3% to 51.3% in patients diagnosed 2008–2010 and 2011–2015, respectively (4). The proportion of patients who received thalidomide, lenalidomide, or bortezomib as part of first-line treatment increased from 17.7% (in 2008) to 54.3% (in 2014) and the use of these drugs was interpreted as a major cause for the observed better survival. In a study from the Thames Cancer Registry in UK, 5-year relative survival was compared in patients diagnosed in 3 calendar periods between 1990 and 2004. Five-year relative survival increased from 36% to 47% in men, and from 40% to 56% in women. The increase was seen in all age groups and was significant also in those 60 years or older (36).

An improvement in relative survival was reported from two regional cancer registries in Northern Netherlands. Five-year relative survival increased in patients younger than 65 years from 34% in those diagnosed 1989–1992 to 56% in those diagnosed 2001–2005. There was no improvement in the older. The authors concluded that the improvement in the younger likely is related to introduction of HDM-ASCT (37). Interestingly, in this study there was a distinct age-related difference in the proportion of patients included in clinical trials. Thirty eight % of patients younger than 65 years were included in clinical trials vs 5% of those 65 years or older.

In a report from the Granada Cancer Registry in Spain, the median overall survival increased from 17.7 months in patients diagnosed 1985–1989 to 34 months in those diagnosed 2005–2009, and was not reached in those diagnosed 2010–2014 (due to short observation time). Relative survival was not reported. Again significant improvements in overall survival was only seen in patients younger than 65 (38).

Survival of multiple myeloma patients did not improve in a study from Japan using data from 6 prefectures covering 13% of the Japanese population and comparing 3 calendar periods 1993–2006. Five-year relative survival in the last period 2003–2006 was only 27.8% which is considerably lower than that reported from U.S. and Europe; however, survival rates were reported combined for all age-groups and there was no age-stratified information on relative survival for younger and older patients. In Japan, thalidomide, bortezomib and lenalidomide were not approved during the period under study (39).

Sub-analysis: single institution studies of trends in survival

There are also a number of studies from single institutions and study groups reporting overall but not relative survival, why it is difficult to exclude some selection bias that limit the generalizability of these results. The Greek Multiple Myeloma Study group compared outcome for patients diagnosed before and after 2000 based on the availability of the so called novel agents after that date. Median overall survival increased from 36 to 48 months but was significantly improved only in those below 65 years. Only 28.2% and 38.3% of

patients respectively were 70 years or older suggesting that older patients may be underrepresented (40).

In a retrospective database analysis including patients treated at the Mayo Clinic between 1971 and 2006, the median overall increased from 29.9 months in patients diagnosed 1971–1996 to 44.8 months in patients diagnosed 1997–2006. When analyzed in 6 calendar periods there was no significant improvement in the two first periods, a trend in patients diagnosed 1995–2000 and significant improvement 2001–2006. In patients 65 years or younger median overall survival increased from 33 months to 65 months while the improvement was modest, from 26 to 32 months in those above 65 years (41). Based on their own retrospective data the authors concluded that the improvement could be related to the introduction of HDM-ASCT and subsequently newer drugs.

In a recent update of the retrospective Mayo Clinic database, overall survival in patients diagnosed in 2001–2005 was compared with those diagnosed 2006–2010. Median overall increased from 4.6 to 6.1 years and 6-year survival from 40% to 51% (42). Interestingly, this improvement was observed only in those 65 years or older. In the Mayo Clinic retrospective database, median age was 66 years and 14% were 75 years or older. In the Swedish prospective, population-based Multiple Myeloma Registry, the median age was 71 years and 24 % were 80 years or older (4). These discrepancies are illustrative of differences in population-based databases (such as the Swedish prospective, population-based Multiple Myeloma Registry) versus tertiary referral single-center databases (such as the retrospective Mayo Clinic database).

Furthermore, in a population-based study conducted in Southern Sweden (the City of Malmö) 2000–2005, the median age at multiple myeloma diagnosis was 74 years and 31% were 80 years or older (3).

Outcome was compared between three successive clinical trials with addition of newer agents in a study from the Multiple Myeloma Institute for Research and Therapy in Arkansas, another tertiary referral single-center databases. Both overall survival and relative survival increased. Estimated 5-year overall survival increased from 50% to 68%. In all these trials patients should be eligible for HDM-ASCT and only 20% were 65 years or older (43).

Five-year overall survival increased from 31.2 to 50.3 months in a study from 18 affiliated hospitals in Japan comparing two calendar periods 1990–2000 and 2001–2012 (44) which should be compared with a 5-year relative survival of 27,8% in a registry-based study from Japan 2003–2006 (39).

Cancer registries usually do not contain information on treatment and improvement of survival over time can only indirectly be linked to introduction of new drugs and procedures.

Several attempts have been made to analyze the effect of treatment on survival in patients outside randomized clinical trials. The impact of novel agents was analyzed in a study from 7 University clinics, 5 regional centers and 3 local hospitals in Sweden. In patients not eligible for HDM-ASCT diagnosed 2000–2011 the median overall survival was 2.8 years.

Among these 29% were treated with bortezomib, thalidomide or lenalidomide in first line with a median overall survival of 4.9 years compared to 2.3 years for those with conventional treatment mostly melphalan and prednisone. However, patients receiving conventional treatment were older and comorbidity was not registered. There was no improvement of overall survival over time (45).

Preliminary data on prevalence

As a consequence of both increasing number of multiple myeloma patients due to ageing populations and improved survival the prevalence of multiple myeloma has increased substantially in many countries. In Sweden, the prevalence increased from 13.1 per 100 000 (in 1980) to 34.8 per 100,000 (in 2014) (6). During the same calendar period, the 5-year relative survival increased from 29% to 49%. Similarly, in Denmark, the prevalence increased more than 3-fold from 1980 to 2012 (46). A large proportion of these patients are elderly with significant age-related comorbidity which, clinically, has direct implications on therapeutic decision making, choice of therapy, and goals of treatment.

Discussion

The multiple myeloma landscape has changed dramatically in the past 50 years. Several studies have reported an increasing age-adjusted incidence during the second half of the 20th Century with a tendency to level-off in the last decades. Other studies based on data from defined populations with a high access to health care and a careful registration system however indicate that the age-adjusted incidence has remained stable and reported increases can be explained by better case ascertainment especially among the elderly. Yet the crude incidence and prevalence has increased dramatically in U.S. and Europe due both to the ageing population and the steep increase in age-specific incidence with advancing age which is even more pronounced in multiple myeloma than in many other cancers and improved survival. Similar changes are to be expected in Asia and Africa. An increasing proportion of multiple myeloma patients are elderly, many of them with age-related comorbidities.

New treatment options have increased survival changing multiple myeloma to a chronic disease and even giving hope of cure as a goal. Significant and sometimes dramatic improvement of both progression-free survival and overall survival has been reported in randomized clinical trials with the introduction of new treatment modalities. However, clinical trials are inherently biased due to the nature of inclusion criteria which limits the possibilities to extrapolate results from clinical trials to the general population. The proportion of patients in the recruitment area that are included in the trials is seldom reported.

Typically, clinical trials do not include older patients or patients with comorbidities. For example, patients with grade 2 polyneuropathy, cardiac disease and not adequate bone marrow reserve were excluded in the pivotal VISTA study showing survival benefit of the addition of bortezomib to the combination of melphalan and prednisone which is commonly used in Europe and Asia. In the VISTA trial, the median age was only 71 years although very few patients below 65 were included (15). Similar exclusion criteria were applied in most other clinical trials. In fact, similar limitations exist also to some extent in reports from

large referral centers. For example, the Mayo Clinic has reported a successive improvement of overall survival, initially restricted to younger patients but recently also in the older (42). The median age of the Mayo Clinic multiple myeloma population was lower than in the Swedish Multiple Myeloma Registry (66 vs. 71 years) and the proportion of elderly lower (14% were 75 years or older in the Mayo Clinic database vs. 24% were 80 years or older in the Swedish Multiple Myeloma Registry). Certainly, these differences will bias the results and limit generalizability of observed results to the general population. To study the impact of the introduction of new treatment modalities on survival in all myeloma patients, data from population-based registries with high coverage and quality are indispensable.

Survival observed in population-based registry studies is generally lower than in randomized clinical trials but yet they show that there has been a steady increase in relative survival that is most likely related to the introduction of HDM-ASCT and later proteasome inhibitors and immunomodulatory drugs. The improvement is most evident in younger patients but has been more modest in older patients, most of whom are not eligible for HDM-ASCT. Also in this group survival is now starting to improve as modern drugs are gradually incorporated in guidelines and used in clinical practice.

The therapeutic arsenal in multiple myeloma is rapidly increasing. The FDA approved four new drugs for the treatment of myeloma in 2015 and expanded label indications in 2. The naked monoclonal antibody daratumumab in combination with dexamethasone and either lenalidomide or bortezomib significantly improved progression-free survival in patients with relapsed or relapsed and refractory myeloma (11, 47). Progression-free survival and overall survival was also significantly prolonged in relapsed/refractory myeloma patients by the combination of lenalidomide and dexamethasone with either the second generation i v proteasome inhibitor carfilzomib (48); the oral proteasome inhibitor ixazomib in combination of lenalidomide and dexamethasone also shows improved progression-free survival (49). Trials are underway of these and other regimes in upfront treatment of multiple myeloma.

The growing evidence that achievement of a high quality response assessed by minimal residual disease (MRD) is associated with improved survival will lead to new strategies with more intensive treatment upfront and hopefully further improve survival (8). Access to drugs varies around the world due to differences in approval and reimbursement systems. Important global challenges include the dilemma with two key aspects: (1) an unmet need for rapid drug development and patient access to new drugs, on one hand; and (2) a need for sustainable costs – both for the individual and society, on the other hand. These are highly complex aspects and there is *not* “one right solution” for every country or region. In our opinion, population-based data will most likely become increasingly important as it can help to guide local decision making and policies.

Summary/Conclusion

The age-adjusted incidence rate of multiple myeloma is stable in populations with good case ascertainment but the crude incidence and prevalence of multiple myeloma as well as the proportion of elderly multiple myeloma patients have increased in U.S. and Europe. We expect to see further increases in crude incidence and prevalence of multiple myeloma in the

coming future which will have an impact on health care plans. New treatments have improved outcome for multiple myeloma patients and 5-year relative survival is now approaching 50 % in the general myeloma population and more than 60% in patients diagnosed below the age of 65 years. However, survival improvements are – so far – less evident in older patients who constitute an increasing proportion of multiple myeloma patients. It is a challenge to design studies that include elderly patients as well as those with more severe comorbidities to better understand how to use novel treatment strategies in these groups. Population-based studies of relative survival are important to fully evaluate the survival impact of new treatments on the whole multiple myeloma population over time.

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Table 1

Populations-based studies on trends in relative survival in multiple myeloma

Reference	Study period	Survival trend[1]	Note
Kristinsson 2007	1973–2003	5-year rel survival from 31 % to 36 %. Improvement only inpatients 60 years or younger	Swedish Cancer Registry
Brenner 2008	1990–2004	5-year relative survival from 28.8% to 34.7%. Improvement mainly in patients 60 years or younger	SEER database
Waxman 2010	1973–2005	5-year rel survival from 26.3% to 35.0% in whites. No significant improvement in blacks.	SEER database
Turesson 2010	1960–2005	Median OS from 24.3 to 56.3 months in patients 65 years or younger. No significant change in those 66 years or older	Information on treatment in individual patients City of Malmö Sweden
Renshaw 2010	1990–2004	5-year relative survival from 36 % to 47% in men and from 40 % to 56% in women.	Thames Cancer Registry database UK
Shaapveld 2010	1989–2005	5-year relative survival from 34 % to 56% in patients < 65 years. No improvement in those 66 years or older.	Two regional cancer centers the Netherlands
Pulte 2011	1973–2007	5-year relative survival from 32.8% to 40.3%. 10-year relative survival from 6.4% to 8.4% in patients 75 year or older	SEER database
Pozzi 2013	1988–2009	5-year relative survival increased from 45.7% to 55.7 %. No significant improvement in patients > 75 years	Modena Cancer Registry
Sant 2014	1997–2008	5-year relative survival increased from 29.8 % to 39.6 %. No significant improvement in patients > 75 years	EUROCARE-5 database
Kristinsson 2014	1973–2009	5-year myeloma-specific survival from 36% to 68 % in patients 50 years or younger, from 34% to 58% in age cohort 51–65, from 26% to 41 % in age cohort 66–79.	Disease-specific survival SEER database
Pulte 2015	2002–2010	5-year relative survival from 47.3% to 53.8% (Germany) and from 39.8% to 54,2% (US)	Patients 75 years or older excluded SEER database and Germany
Rios-Tamayos 2015	1985–2009	Median OS from 17.7 months to 34 months. Improvement restricted to younger patients.	Granada Cancer Registry Spain
Chihara 2015	1993–2006	No change in 5-year relative survival – from 30.0% to 27.8 %.	6 prefectures in Japan covering 13.4% of the Japanese population. Thalidomide, bortezomib and lenalidomide not approved during the study period.
Jansen 2015	2002–2010	5-year relative survival increased from 39,9% to 47,9 %	11 population-based cancer registries in Germany
Costa 2017	1993–2012	5-year relative survival from 36.3% to 61.8% in patients < 65 years, from 29.0% to 48.5% in age cohort 65–74 years and from 21.1% to 34.0% in age cohort 75 years or older.	SEER database
Blimark 2017	2008–2014	5-year relative survival increased from 47.3 % to 51.3 %	Swedish Myeloma Registry
Thorsteinsdottir 2018	1973–2013	5-year relative survival increased from 28% to 41%	Swedish Cancer Registry

[1] Comparison of survival for patients diagnosed in the first vs the last calendar period in each study.

[2] Two studies that reported observed survival and one study reporting myeloma-specific survival included.