IMPORTANCE The outcome of older patients with acute myeloid leukemia (AML) remains unsatisfactory. Recent studies have shown that HLA-mismatched microtransplant could improve outcomes in such patients.

OBJECTIVE To evaluate outcomes in different age groups among older patients with newly diagnosed AML who receive HLA-mismatched microtransplant.

DESIGN, SETTING, AND PARTICIPANTS This multicenter clinical study included 185 patients with de novo AML at 12 centers in China, the United States, and Spain in the Microtransplantation Interest Group. Patients were divided into the following 4 age groups: 60 to 64 years, 65 to 69 years, 70 to 74 years, and 75 to 85 years. The study period was May 1, 2006, to July 31, 2015.

EXPOSURES Induction chemotherapy and postremission therapy with cytarabine hydrochloride with or without anthracycline, followed by highly HLA-mismatched related or fully mismatched unrelated donor cell infusion. No graft-vs-host disease prophylaxis was used.

MAIN OUTCOMES AND MEASURES The primary end point of the study was to evaluate the complete remission rates, leukemia-free survival, and overall survival in different age groups. Additional end points of the study included hematopoietic recovery, graft-vs-host disease, relapse rate, nonrelapse mortality, and other treatment-related toxicities.

RESULTS Among 185 patients, the median age was 67 years (range, 60-85 years), and 75 (40.5%) were female. The denominators in adjusted percentages in overall survival, leukemia-free survival, relapse, and nonrelapse mortality are not the sample proportions of observations. The overall complete remission rate was not significantly different among the 4 age groups (75.4% [52 of 69], 70.2% [33 of 47], 79.1% [34 of 43], and 73.1% [19 of 26]). The 1-year overall survival rates were 87.7%, 85.8%, and 77.8% in the first 3 age groups, which were much higher than the rate in the fourth age group (51.7%) (P = .004, P = .008, and P = .04, respectively). The 2-year overall survival rates were 63.7% and 66.8% in the first 2 age groups, which were higher than the rates in the last 2 age groups (34.2% and 14.8%) (P = .02, P = .03, P < .001, and P < .001, respectively). The 1-year cumulative incidences of nonrelapse mortality were 10.2%, 0%, 3.4%, and 26.0% in the 4 age groups and 8.1% in all patients. The median times to neutrophil and platelet recovery were 12 days and 14 days after induction chemotherapy, respectively. Five patients had full or mixed donor engraftment, and 30.8% (8 of 26) of patients demonstrated donor microchimerism. Two patients (1.1%) developed severe acute graft-vs-host disease.

CONCLUSIONS AND RELEVANCE Microtransplant achieved a high complete remission rate in AML patients aged 60 to 85 years and higher 1-year overall survival in those aged 60 to 74 years.
Older patients (≥60 years) with acute myeloid leukemia (AML) have a lower complete remission (CR) rate and higher mortality after standard treatments because of intrinsic drug resistance related to poor-risk cytogenetics as well as unique biology, with different molecular drivers evident compared with younger patients.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\) Induction chemotherapy with standard-dose cytarabine hydrochloride in combination with an anthracycline aims at reducing the tumor burden but confers a risk of organ toxicities. Although chemotherapy with attenuated doses decreases organ toxicities, it has reduced ability to kill leukemic cells and is associated with low CR rates and poor short-term survival.\(^3\)\(^4\)\(^5\)\(^6\) Higher doses of daunorubicin hydrochloride result in greater response rates compared with conventional doses, but the benefits in older patients with AML are limited mainly to patients younger than 70 years.\(^5\)\(^6\)\(^7\) Although allogeneic transplant has been used successfully to cure both younger and older patients with AML, it is often limited by the high incidence of nonrelapse mortality (NRM) and severe toxicities, even with nonmyeloablative conditioning or reduced-intensity conditioning regimens.\(^8\)\(^9\)\(^10\)\(^11\)

Primary clinical studies\(^12\)\(^13\)\(^14\) have shown that infusion of HLA-mismatched donor granulocyte-colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells (GPB-SCs) combined with chemotherapy (microtransplant [MST]) increased CR rates, improved survival, and avoided graft-vs-host disease (GVHD) in small cohorts of older patients with AML. However, studies involving larger cohorts and multicenter experience with MST in older patients are scarce.

In the present study, we identified 185 patients aged 60 to 85 years with newly diagnosed AML undergoing HLA-mismatched MST at 12 centers in China, the United States, and Spain in the Microtransplantation Interest Group. These include the following: (1) Department of Hematology and Transplantation, Affiliated Hospital of The Academy of Military Medical Sciences, Beijing, China; (2) Division of Hematologic Malignancies and Cellular Therapy, Department of Medicine, Duke University, Duke Cancer Institute, Durham, North Carolina; (3) Department of Hematology, Jiangsu Province People’s Hospital, Nanjing, China; (4) Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, Keck School of Medicine of University of Southern California, Los Angeles; (5) Department of Haematology, Hospital Universitario Puerta de Hierro, Majadahonda, Comunidad de Madrid, Spain; (6) Department of Hematology, The Second Artillery General Hospital, Beijing, China; (7) Department of Hematology, He Ping Central Hospital of the Changzhi Medical College, Changzhi, China; (8) Department of Hematology, Central Hospital of Xinxing City, Xinxiang, China; (9) Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China; (10) Department of Hematology, The Fourth Military Medical University, Xi’an, China; (11) Department of Hematology, The Second Affiliated Hospital of Shaxi University, Taiyuan, China; and (12) Department of Hematology, Central Hospital of Hefei City, Hefei, China. The primary end point of the study was to evaluate CR rates, leukemia-free survival (LFS), and overall survival (OS) in different age groups. Additional end points of the study included hematopoietic recovery, GVHD, relapse rate, NRM, and other treatment-related toxic effects.\(^8\)\(^12\)\(^14\)

### Methods

#### Patients and Donors

From May 1, 2006, to July 31, 2015, patients aged 60 to 85 years with de novo AML were included in the study at 12 centers coordinated through the Department of Hematology and Transplantation, Affiliated Hospital of The Academy of Military Medical Sciences, Beijing, China. The diagnoses were defined by the treating institution according to the French-American-British and World Health Organization criteria,\(^15\) and the prognostic risk groups (standard-risk or high-risk cytogenetics) were defined according to the NCCN 2012 criteria.\(^16\) Cytogenetic studies on pretreatment bone marrow samples were performed according to the International System of Human Cytogenetic Nomenclature.\(^17\) Screening for molecular markers AML1-ETO (OMIM 151385) and CBFB-MYH11 (OMIM 121360) was performed universally, while NPM1 (OMIM 164040), FLT3-ITD (OMIM 136351), CEBPA (OMIM 116897), MLL-PTD (OMIM 159555), TET2 (OMIM 612839), and DNMT3A (OMIM 602767) gene detection was performed only after October 2008. Patients with acute promyelocytic leukemia or with a blast crisis of chronic myeloid leukemia, a Karnofsky score less than 60%, or pulmonary diffusion capacity less than 35% were excluded, while those with secondary AML or chronic myelomonocytic leukemia were included. Patients with a suitable fully matched sibling or unrelated donor were also excluded. Of the 202 older patients with de novo AML screened, 185 patients were enrolled in the present study, and the other 17 patients were excluded because of patient refusal (n = 3), donor refusal (n = 4), other nonprotocol treatment (n = 9), or death before the first induction chemotherapy (n = 1). The 185 included patients were divided into the following 4 age groups: 60 to 64 years, 65 to 69 years, 70 to 74 years, and 75 to 85 years. Among the 185 patients, 24 were included in a previous study,\(^12\) but updated data were added to the present study. Another 6
patients were excluded from this study because of age older than 85 years (n = 2) or enrollment outside of the study period (n = 4).

The study protocol, including inclusion and exclusion criteria and protocol implementation, was approved by the Human Ethics Committee of the Affiliated Hospital of The Academy of Military Medical Sciences and at each study site and was in accord with the Declaration of Helsinki. All patients and their donors provided written informed consent before the study. The patients were treated according to preregistered protocols.

**Treatment Design**

**Induction Chemotherapy**

Induction chemotherapy mainly consisted of daunorubicin hydrochloride (45-60 mg/m²), mitoxantrone hydrochloride (8-12 mg/m²), or idarubicin hydrochloride (8-12 mg/m²) for 3 days in combination with cytarabine (100-150 mg/m²) for 7 days (n = 161), followed by an infusion of GPBSCs 24 hours (day 0) after the completion of cytarabine. Other induction chemotherapy included the combination of decitabine (10 mg/m²) for 5 days, cytarabine (10 mg/m²) every 12 hours for 14 days, aclarubicin (14 mg/m²) for 4 days, and additional G-CSF (200 μg/m²) for 14 days (DAAG) (n = 24), followed by an infusion of GPBSCs 24 hours (day 0) after the completion of cytarabine. If the patients failed to achieve CR after the first cycle of induction chemotherapy, a second cycle of the same induction chemotherapy was permitted.

**Postremission Therapy**

Patients who achieved CR received 2 to 3 courses of MST as postremission therapy, which consisted of intermediate-dose cytarabine (1.0 g/m² for 6 doses) (n = 125) or DAAG chemotherapy (n = 13), followed by an infusion of GPBSCs after cytarabine chemotherapy, with up to 3-month intervals between the courses. None of the patients received any GVHD prophylaxis or further maintenance therapy. Infection prophylaxis and support treatment, including G-CSF, were administered according to each institution's standard practice guidelines.

A recommended dose adjustment was followed. For patients with a creatinine clearance rate decreasing to less than 60 mL/min/1.73 m² (to convert creatinine clearance rate to milliliters per second per meter squared, multiply by 0.0167) or for those in the third and fourth age groups, the doses of daunorubicin and cytarabine were reduced to 2 days and 5 days, respectively, during induction chemotherapy, and the dose of cytarabine was reduced to 500 mg/m² for 6 doses during postremission therapy.

**Apheresis of Donor Peripheral Mononuclear Cells**

Mobilization and apheresis of HLA-mismatched donor peripheral mononuclear cells were performed as previously described. Fresh donor cells were used in the first induction chemotherapy, and other donor cells were divided into small packs and cryopreserved in liquid nitrogen for second induction chemotherapy or postremission therapy.

Before transplant, the donor and recipient HLA-A (OMIM 142800), HLA-B (OMIM 142830), HLA-C (OMIM 142840), HLA-DRB1 (OMIM 142857), and HLA-DQB1 (OMIM 604305) alleles were genotyped using the polymerase chain reaction-sequence-specific primer method. For patient and donor pairs who had more related and matched HLA loci, matched red blood cell type and cytomegalovirus-seronegative donors were chosen first; however, donor sex and other characteristics were not considered a priority. If patients had no available related donor, an HLA-mismatched unrelated donor was used.

**Detection of Donor Chimerism and Microchimerism**

Full donor chimerism and mixed chimerism were detected by short tandem repeat–polymerase chain reaction assay as previously described. For microchimerism detection (donor cells <1%), only 26 female patients who had a male donor and sufficient samples were monitored as previously described.

**Response Criteria and Outcome Evaluation**

Outcome data were evaluated through December 30, 2015. Patient responses, including CR, LFS, OS, and NRM, were determined according to the revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Acute GVHD and chronic GVHD were defined according to published criteria. Monitoring for relapse was performed according to institutional guidelines. The median relapse time was defined as the median time from CR to relapse. Early death was defined as death within 4 weeks after initiation of induction chemotherapy.

**Statistical Analysis**

Variables related to clinical characteristics between age groups were compared using χ² test. Survival data were analyzed by the log-rank test, and survival curves were prepared using the Kaplan-Meier method. Cox proportional hazards regression models were applied to evaluate the relative factors for LFS, OS, NRM, and relapse. The denominators in adjusted percentages in OS, LFS, relapse, and NRM are not the sample proportions of observations. Statistical significance was defined as 2-sided P < .05. A software program (SPSS, version 17.0; SPSS Inc) was used in all statistical analyses.

**Results**

**Patient Characteristics**

Among 185 patients with de novo AML at 12 centers in China, the United States, and Spain, the median age was 67 years (age range, 60-85 years), and 75 (40.5%) were female. eTable 1 in the supplement lists demographic and disease characteristics before transplant, stratified by age group. There were no statistically significant differences among the 4 age groups except for the donor and recipient HLA-mismatched loci; the fourth age group had fewer patients but many more donors and recipients with HLA-mismatched loci 7 through 10 compared with the other age groups.
Response to Induction Chemotherapy
The overall CR rate was 74.6% (138 of 185). The CR rate did not significantly differ among the 4 age groups (75.4% [52 of 69], 70.2% [33 of 47], 79.1% [34 of 43], and 73.1% [19 of 26]) (Table 2 in the Supplement). There were no significant differences in the CR rate among different centers or induction chemotherapy regimens. The CR rate was lower in the high-risk group compared with the standard-risk group (66.7% [60 of 90] and 82.1% [78 of 95], respectively) (P = .02).

Hematopoietic Recovery and Toxicity
The median times to neutrophil and platelet recovery were 12 days and 14 days after induction chemotherapy, respectively, with no significant differences among the 4 age groups. The overall rates of severe infection and organ failure were 8.0% (11 of 138) and 2.2% (3 of 138), respectively, with no significant differences among the 4 age groups.

OS and LFS
Of the 138 patients who achieved CR, 98 (71.0%) finished 2 or 3 consolidation courses, including 44 (31.9%), 25 (18.1%), 23 (16.7%), and 6 (4.3%) in the 4 age groups. The other 40 patients (29.0%) finished one course or none, including 8 (5.8%), 8 (5.8%), 11 (8.0%), and 13 (9.4%) in the 4 age groups.

The median follow-up time was 14 months (range, 1-106 months). The median OS times were 16, 14, 13, and 10 months in the 4 age groups. The 1-year OS rate was much lower in the fourth age group (51.7%) than rates in the first 3 age groups (87.7%, P = .004, 85.8%, P = .008, and 77.8%, P = .04, respectively) (Figure 1A). The 2-year OS rate was 63.7% in the first age group, which was higher than the rates in the third (34.2%) (P = .02) and fourth (14.8%) (P < .001) age groups. Similarly, the second age group also had higher 2-year OS rate (66.8%) compared to the third (P = .03) and fourth (P < .001) age groups.

The overall 1-year LFS rate was 64.9% in the first age group, which was much higher than the rates in the third (35.4%) (P = .02) and the fourth (21.7%) (P < .001) age groups. Similarly, the second age group also had much higher 1-year LFS rates (73.8%) compared to the third (P = .01) and fourth (P = .002) age groups (Figure 2A). The 2-year LFS rate was 51.0% in the first age group, which was much higher than the rates in the third (25.3%) (P = .02) and the fourth (14.5%) (P = .002) age groups. Similarly, the second age group also had much higher 2-year LFS rate (59.1%) compared to the third (P = .009) and fourth (P = .001) age groups.

NRM and Relapse
The median relapse time was 8.5 months (range, 1.5-62 months). The 1-year cumulative incidence of relapse in the first age group (23.2%) was much lower than the rates in the third (58.2%) (P < .001) and the fourth (69.0%) (P = .002) age groups. Similarly, the second age group also had much lower 1-year cumulative incidence of relapse (22.9%) compared to the third (P = .02) and fourth (P = .03) age groups. There was no significant difference in the 2-year cumulative incidences of relapse between the first 2 age groups (97.9% and 32.5%) (P = .99), however, the third age group had much higher 2-year cumulative incidence of relapse (70.1%) compared to the first (P < .001) and second (P = .01) age groups.

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Figure 1. Overall Survival of Older Patients With Acute Myeloid Leukemia After Microtransplant

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Similarly, the fourth age group also had much higher 2-year incidence of relapse (79.3%) compared to the first (P < .001) and second (P = .02) age groups (Figure 3A).
The overall NRM was 10.1%. The 100-day cumulative incidences of NRM were 1.9%, 0%, 0%, and 5.6%, with no significant differences among the 4 age groups. The 1-year cumulative incidences of NRM were 8.1% in all patients aged 60 to 85 years and 10.2%, 0%, 3.4%, and 26.0% in the

A, Leukemia-free survival of the patients according to 4 age groups. B, Patients who received 2 or 3 courses of postremission therapy had much higher 2-year leukemia-free survival compared with those who received one course or none. C, Patients in the high-risk group had lower 2-year leukemia-free survival compared with the standard-risk group. del Indicates deleted.

A, Relapse incidence of the patients according to 4 age groups. B, Patients who received 2 or 3 courses of postremission therapy had much lower relapse rates compared with those who received one course or none. C, Patients in the high-risk group had a higher relapse rate compared with the standard-risk group. del Indicates deleted.
4 age groups, with no significant differences between the first and fourth age groups. The 2-year cumulative incidences of NRM were also comparable among the 4 age groups (17.2% vs 7.7% vs 12.2% vs 26.0%) (P = .06) (Figure 4A).

**Donor Chimerism and Microchimerism**

Of the 185 patients, 2.7% (5 of 185) established full or mixed chimerism. Only 2 patients demonstrated stable full donor chimerism, and 3 patients developed mixed chimerism. Of the 26 patients who had an informative SRY (OMIM 480000) gene, 8 (30.8%) developed donor microchimerism, with a range of 0.0000151 to 0.0989 copies of gene expression. Assessed kinetics of donor microchimerism showed that microchimerism emerged on day 2 and reached its peak on days 7 to 10 after the MST treatment. Among the 8 patients, the donor microchimerism remained for longer than 10 months in 1 patient, longer than 6 months in 2 patients, and longer than 2 months in 1 patient and remained for shorter than 2 weeks in 4 patients.

**Graft-vs-Host Disease**

Only 2 patients (1.1%) were diagnosed as having severe acute GVHD because of high fever, location of rash on the neck, and severe hyperbilirubinemia after neutrophil recovery and transient full donor engraftment after MST (biopsies were not performed). The patients failed to respond to anti-GVHD treatment and died of multiorgan failure at days 36 and 39, respectively, after MST. No definite clinical acute or chronic GVHD was observed in any other patients.

**Multivariable Analysis**

On multivariable analysis of the factors influencing LFS, OS, and relapse, such as patient and donor age, sex, HLA-mismatching loci, related or unrelated donor, infused CD34+ cell dose, CD3+ cell dose, mononuclear cell dose, natural killer cell dose, and KIR (OMIM 604946) gene expression of natural killer cells, only the number of postremission therapy courses and cytogenetic and molecular risk groups were identified as prognostic. Patients who received 2 or 3 courses of postremission therapy had much higher 2-year OS (61.3% [69 of 98]) (Figure 1B), higher LFS (47.5% [60 of 98]) (Figure 2B), and lower relapse rates (39.7% [29 of 98]) (Figure 3B) compared with those who received one course or none (11.1%, P < .001, 7.8%, P < .001, and 89.4%, P < .001, respectively), although there was no significant difference in 100-day NRM (1.0% vs 2.6%) (P = .50) and 1-year NRM (6.4% vs 13.5%) (P = .21) (Figure 4B). Similarly, patients in the high-risk group had lower 2-year OS (34.3% [31 of 90]) (P = .004) (Figure 1C) and LFS (28.5% [26 of 60]) (P = .007) (Figure 2C) but a slightly higher relapse rate (61.5% [22 of 60]) (P = .21) (Figure 3C) compared with the standard-risk group (62.3% [57 of 78], 52.0% [49 of 78], and 43.1% [26 of 78], respectively).

**Discussion**

The present study reports long-term outcomes among 185 patients aged 60 to 85 years with newly diagnosed AML who received HLA-mismatched MST in multiple centers from the Microtransplantation Interest Group. The overall CR rate was 74.6% (138 of 185), and OS rates at 1 year and 2 years were 79.9% and 50.2%, respectively (eTable 2 in the Supplement), suggesting encouraging therapeutic results, with a higher CR rate and longer survival compared with standard care in older patients. It has been demonstrated that the major reasons for initial treatment failure in older patients with AML are the high early mortality and delayed hematopoietic recovery. In a report from a Swedish population registry that included 3371 patients with AML, CR rates among intensively treated patients were found to decrease with age. Löwenberg et al demonstrated that patients between ages 60 and 65 years can benefit from high-dose daunorubicin hydrochloride (90 mg/m^2), while the United Kingdom National Cancer Research Institute AML17 trial showed no definite evidence of benefit in older patients. In the present multicenter study, the overall CR rate was as high as 74.6% (138 of 185). Notably, not only patients aged 60 to 69 years (75.4% [52 of 69] in the first age group
and 70.2% [33 of 47] in the second age group) but also those aged 70 to 85 years tolerated MST with induction chemotherapy and achieved high CR rates (79.1% [34 of 43] in the third age group and 73.1% [19 of 26] in the fourth age group), with rapid hematopoietic recovery. In addition, the overall CR rate reached 66.7% (60 of 90) in the high-risk group, although it was much lower than that in the standard-risk group (82.1% [78 of 95]) (P = .02).

The best standard postremission therapeutic options for older patients with AML remain uncertain, and survival is still unsatisfactory. The Swedish group reported that 2-year OS and LFS were 25% and 22%, respectively, in patients with AML older than 65 years who received medium-dose cytarabine as postremission therapy. In patients with AML older than 60 years undergoing T-cell-repleted haploidentical hematopoietic cell transplant, Kasamon et al reported that 3-year OS was 38%. In the present study, in older patients with AML who received medium-dose cytarabine with MST as postremission therapy, overall 2-year OS and LFS were 50.2% and 42.1%, respectively, which not only included patients aged 60 to 64 years and 65 to 69 years but also those aged 70 to 74 years, among whom 1-year OS was 87.7%, 85.8%, and 77.8%, respectively, suggesting that MST may offer an effective and safe postremission therapy approach in older patients.

It has been known that infusion of allogeneic immune cells can mediate a direct or indirect cytotoxic effect. In the present study, a large number of HLA-mismatched donor T cells (up to 8.4 × 10^8/kg) and other immune cells were infused, which may have important roles in improving outcomes by strengthening immunological cytotoxic antileukemic effects based on the chemotherapy. The smaller number of CD34+ cells that were infused may also speed hematopoietic recovery.

While MST achieved a high CR rate and 1-year survival in 4 age groups, the leukemia relapse rate was much higher, especially for the patients aged 75 to 85 years, who are considered “very old” patients with AML. Unlike the other age groups, these patients received a reduced chemotherapy dose, and half of them completed either one postremission course or none. Overall 1-year and 2-year relapse rates were 69.0% and 79.3%, respectively, among the very old patients, which were much higher compared with the other age groups, although 100-day NRM (5.6%) was comparable to rates of the other age groups. Otherwise, the patients who received 2 or 3 courses of postremission therapy had a much higher 2-year OS (61.3% vs 11.1%) (P < .001) and lower relapse rate (39.7% vs 89.4%) (P < .001) than those who received one course or none. These data suggest that the main reasons for high relapse rates in very old patients with AML may be related to lack of sufficient postremission therapy as well as reduced chemotherapy dose. Therefore, reducing postremission therapy courses or chemotherapy dose simply because of patient age may not be advisable for older patients.

Studies have shown that most patients with AML could achieve full donor chimerism or convert to full donor chimerism from mixed chimerism after hematopoietic stem cell transplant; however, severe GVHD remained a major complication, particularly in HLA-mismatched transplant. In the present MST study, 2.7% (5 of 185) and 30.8% (8 of 26) of patients developed full or mixed chimerism and microchimerism, respectively, because no lymphoablative conditioning was used. Notably, only 2 patients (1.1%) developed severe acute GVHD, although all patients received cell infusions from HLA-mismatched donors, including 9 with unrelated and 0 of 10 HLA-matched unrelated donors, and no GVHD prophylaxis was used. The extremely low GVHD incidence contributed significantly to reducing NRM and improving survival.

Limitations

A limitation of this study is the absence of randomized groups, such as reduced-intensity or nonmyeloablative conditioning transplant recipients, although a randomized clinical trial would be much more difficult to implement in older patients, especially for those older than 75 years. A prospective, randomized, phase 3 confirmatory study comparing this approach with chemotherapy only is also under way by the International Microtransplantation Cooperative Group.

Conclusions

Clinical results suggest that MST is a safe, practical, and reproducible therapy in older patients newly diagnosed as having AML. Our findings showed that this approach achieved high CR rates in patients with AML aged 60 to 85 years and higher 1-year OS in those aged 60 to 74 years.
Mohrbacher, and Krakow were co–first authors and co–last authors of the manuscript for publication.

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REFERENCES


