Adjuvant chemotherapy in average-risk adult medulloblastoma patients improves survival: a long term study

Enrico Franceschi (enricofra@yahoo.it)
Azienda Unita Sanitaria Locale di Bologna
Santino Minichillo
Azienda Unita Sanitaria Locale di Bologna
Antonella Mura
Azienda Unita Sanitaria Locale di Bologna
Alicia Tosoni
Azienda Unita Sanitaria Locale di Bologna
Maurizio Mascarin
Aviano Air Base
Chiara Tomasello
Azienda Unita Sanitaria Locale di Modena
Stefania Bartolini
Azienda Unita Sanitaria Locale di Bologna
Alba Ariela Brandes
Azienda Unita Sanitaria Locale di Bologna

Research article

Keywords: Medulloblastoma, chemotherapy, survival, average-risk

Posted Date: March 18th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17890/v1

Version of Record: A version of this preprint was published on August 12th, 2020. See the published version at https://doi.org/10.1186/s12885-020-07237-x.

Abstract

Background : The role of chemotherapy for average-risk adult patients remains controversial. Medulloblastoma is extremely rare in adults. Radical surgery and radiotherapy provide a significant control of disease and a good prognosis but about 25% of average-risk patients have a relapse and die because of disease progression. No data in average-risk adult patients on a direct comparison between radiotherapy alone and radiotherapy plus chemotherapy

Methods : We analyzed 48 average-risk patients according to Chang classification diagnosed from 1988 to 2016.

Results : Median age was 29 years (range 16-61). Main histology type were classic in 15 patients (31.3%) and desmoplastic in 15 patients (31.3%), 5 patients had extensive nodularity (10.4%) and 2 patients had large cells/anaplastic histology (4.2%). Twenty-four patients (50%) received adjuvant radiotherapy alone and 24 (50%) received radiotherapy and chemotherapy. After a median follow-up of 12.5 years, we found that chemotherapy increases PFS (PFS-15 82.3 ± 8.0% in RT-CT group vs. 38.5% ± 13.0% in RT group p=0.05) and OS (OS-15 89.3% 7.2% vs. 52.0% 13.1%, p=0.02). Among patients receiving chemotherapy, the reported grade ≥ 3 adverse events were: 9 cases of neutropenia; 6 cases of G3 neutropenia (25%) and 3 cases of G4 neutropenia (13%), 1 case of G3 thrombocytopenia (4%) and 2 cases of G3 nausea (8%).

Conclusions : Our study with a long follow up period suggests that adding adjuvant chemotherapy to radiotherapy might improve PFS and OS in average-risk adult medulloblastoma patients

Background

Medulloblastoma is rare in adults (less than 1% of primitive CNS tumors) for whom its incidence is 0.6–1 case per million per year. It is diagnosed 1.58 times more frequently in males than females during childhood, but this difference seems not confirmed in adults (1–3).

Correct staging is an important prognostic factor by influencing therapeutic program. Fundamental staging examinations are brain/spinal MRI before and after (48 hours) surgery and CSF cytology performed 15–20 days after surgery. Tumors are classified for their extension and site of origin (T) and absence or presence of metastasis inside or outside the neuraxis (M) according to Chang's staging system (4). Tumor assessment should follow neuroradiologic criteria established by Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group (5). Correctly staged, patients are usually divided into average and high risk groups.

The average-risk group presents no metastasis (M0) and no residual disease after surgery (residual disease has been defined > 1.5 cm^2). High-risk patients have metastases and/or residual disease and often unfavorable histology (large cells/anaplastic) (3).

The treatment for pediatric average-risk patients, given the long life expectancy, is limited by long term toxicity related to radiotherapy which can compromise their neurological and intellectual development. To avoid this toxicity, in different clinical trials, clinicians have tried to reduce RT doses by associating chemotherapy and, following the good results of his trial, Packer et al. proposed a schedule which is now considered the standard treatment of pediatric average-risk population (7;8).

The role of chemotherapy for average-risk adult patients remains controversial. Medulloblastoma is rare in adults and, therefore, it is extremely difficult to accrual in clinical trials. Radical surgery and radiotherapy represent the standard treatment with a 5-years progression free survival (PFS) rate of 72% and 5-years OS rate of 75% (3). Despite this good prognosis, about 25% of average-risk patients have a relapse and die because of progression disease (3). In literature, there are no data if adding chemotherapy to radiotherapy plus chemotherapy improves the results.

Therefore, the possibility to associate chemotherapy to the standard treatment is still an open question and currently adjuvant chemotherapy could be evaluated in poor risk histologies (large cells/anaplastic).

On the basis of this open question, we performed a retrospective analysis about outcomes of consecutive average-risk adult patients followed in our Institution and treated with radiotherapy alone or with radiotherapy plus chemotherapy.

Methods

Patients included in our data warehouse were ≥ 16 years of age, had histologically confirmed medulloblastoma and underwent adjuvant radiotherapy with or without chemotherapy. Average-risk was defined as postsurgical residual ≤ 1.5 cm^2 and no metastatic disease (M0) according to Chang's classification.

The patients were staged with brain MRI and, whenever possible, also spine MRI before surgery. In all patients postsurgical MRI with contrast enhancement was routinely used to define residual disease within 48–72 hours from surgery. Spine MRI was performed after surgery if not available before. CSF cytology was obtained at least 15 days far from surgery. Radiotherapy was administered with the dose of 36 Gray (Gy) in 20 fractions on the cranio-spinal axis plus a boost of 18 Gy in 10 fractions on the posterior cranial fossa (total dose 54 Gy). Chemotherapy regimens were: cisplatin (25 mg/ m^2 on days 1–4) plus etoposide (40 mg/ m^2 on days 1–4) or carboplatin (300 mg/m^2 on day 1) plus etoposide (60 mg/ m^2 on days 1–3).

We included 48 average-risk patients diagnosed from 1988 to 2016. Median age was 29 years (range 16–61), M/F ratio was 26 (54.2%)/22 (45.8%). The most represented histologies were classic in 15 patients (31.3%) and desmoplastic in 15 patients (31.3%). 5 patients had a extensive nodularity (10.4%) and 2 patients had large cells/anaplastic histology (4.2%).

The patients were homogeneously distributed on two groups: 24 (50%) received only adjuvant radiotherapy and 24 (50%) received also chemotherapy. Patients' characteristics are summarized in Table 1.

Statistical analysis

Data are reported as means, ranges and frequencies. Survival data were computed through Kaplan-Meier procedure and were analyzed by means of the log-rank test. PFS and OS were computed from the time of surgery to the first progression or death, respectively, or to the date of the last follow-up or contact. The SPSS (Version 13.0 for Windows; SPSS Inc., Chicago, IL, USA) was used as statistical package. Two-tailed P values less than 0.05 were considered significant.

Results

Survival

After a median follow-up of 151.5 months (95% CI 124.5–178.5), 14 patients had disease progression and 10 patients died, 9 for disease and 1 for other causes (considered censored at the time of the event). Relapse sites were spinal, bone, cerebellum and brain.

Progression-free survival

Median PFS was 9 years in patients who received radiotherapy (RT) and not reached in those who received RT and chemotherapy (CT). We found that adding chemotherapy increases PFS (HR 0.334; 95% CI 0.105–1.068, p = 0.05). This benefit was greater after 10 years from diagnosis: the percentage of patients without progression at 10 and 15 years (PFS-10 and 15) was 82.3% ± 8.0% in the RT-CT group versus (vs.) 38.5% ± 13.0% in the RT group (table2).

Overall survival

Median OS was 18 years (95% CI 89.0–344.1) in patients who received RT alone and was not reached for patients treated with RT and CT but there was a survival benefit in adding chemotherapy (HR 0.187; 95% CI 0.040–0.872, p = 0.02). This benefit was considerable with a longer follow up: the percentage of patients alive at 10 and 15 years (OS-10 and OS-15) were 89.3% ± 7.2% (CT-RT group) vs. 74.1% ± 10.3% (RT group) and 89.3% ± 7.2% (CT-RT group) vs. 52.0% ± 13.1% (RT group) respectively (table 2). Survival curves are reported in Fig. 1and Fig. 2.

Safety

Data on toxicities are available for all patients. Toxicities were classified according to CTCAE v4.0. Among patients receiving chemotherapy, the reported grade ≥ 3 adverse events were: 9 cases of neutropenia and, particularly, 6 cases of G3 neutropenia (25%) and 3 case of G4 neutropenia (13%), 1 case of G3 thrombocytopenia (4%) and 2 cases of G3 nausea (8%). Grade ≥ 3 toxicities related to radiotherapy alone were: 1 case of G3 hearing loss(4%), 2 cases of G3 neutropenia (8%) and 2 cases of

G3 thrombocytopenia (8%). Endocrinopathy (mild increase in TSH and prolactin) was found in only a patient treated with RT alone. No secondary malignancies were reported.

Discussion

In average-risk patients the standard treatment includes radical surgery and radiation therapy. In the management of young average-risk medulloblastoma patients, the possibility of adding chemotherapy has been regarded as an attempt to reduce total dose of RT delivered to brain and spinal cord and to limit toxic effects and long-term sequelae such as growth, neuro-cognitive and endocrinologic impairment. Packer et al. reported positive results in their trial in which children with non-disseminated medulloblastoma were treated with postoperative reduced-dose craniospinal irradiation (23.4 Gy in 13 fractions) with a boost to the posterior fossa (31.8 Gy in 17 fractions) with concomitant vincristine and adjuvant chemotherapy with lomustine, vincristine and cisplatin. They reported PFS rates at 3 and 5 years of 86% and 79% respectively, which are comparable with those obtained with full-dose radiotherapy alone. This schedule resulted in better tolerance and good safety and it currently represents the standard treatment of average-risk patients older than 3 years and younger than 18 years (7;8).

In average risk adult population, the role of chemotherapy is still matter of debate.

Due to the rarity of the disease in adults, data in literature are few and derive mostly from retrospective and small series studies (9). Randomized trials are not available.

Moreover, a long follow up period is needed to evaluate both PFS and OS.

Thus, data from retrospective studies including patients with homogeneous treatments and a long follow up period are essential to provide data.

A large retrospective analysis by Padovani et al. found no survival difference between average-risk patients treated with radiotherapy alone (axial doses $\geq$ 34 Gy) and patients treated with radiotherapy in combination to chemotherapy (axial doses $<$ 34 Gy). This study was limited by heterogeneous chemotherapeutic regimens and data collected from different centers (10).

The role of chemotherapy is controversial due to high toxicity and the absence of randomized trials in average risk setting.

Greenberg et al. in 2001 published the results of their study on 17 average and high-risk patients treated with radiotherapy associated to Packer's chemotherapeutic regimen. They failed to show that chemotherapy is effective when added to craniospinal radiation in adult patients with medulloblastoma. Relapse-free survival and overall survival did not reach statistical significance. Furthermore, the patients experienced considerably greater chemotherapy-related toxicity than did children treated on an identical protocol (11). In a study by Friedrich et al. adult patients were treated with lomustine, vincristine and cisplatin for 8 cycles after RT according to the HIT 2000 protocol. In this study the incidence of grade $\geq$ 3 hematological adverse events was 58% and grade $\geq$ 2 neurotoxicity was 69%. More than half of patients

were not able to perform the planned 8 cycles and experienced dose delays and reductions (12). In NOA-07 multicenter pilot study 25 adult patients received combined craniospinal irradiation with vincristine followed by 8 cycles maintenance chemotherapy with cisplatin, lomustine and vincristine. Seventy percent of patients tolerated 4 cycles of chemotherapy, but treatment was withdrawn or dose was reduced in almost 60% of patients after cycle 4 due to side effects. Leucopenia and thrombocytopenia were the any grade major toxicity. Polyneuropathy and ototoxicity were the only grade 3 and 4 non hematological toxicities (40% of patients). The authors concluded that this regimen was not feasible in adult patients (13).

About chemotherapeutic schedules, we found that cisplatin or carboplatin plus etoposide have a favorable toxicity profile, avoiding hematologic toxicities due to the cumulative dose of nitrosoureas and are more feasible in adult than pediatric protocols (3; 14–15).

In our previous study we showed a trend for improved OS for average risk patients treated with chemotherapy after a median follow up of 10 years ($p = 0.079$)(16).In the present study with more patients and a longer follow up time we showed a statistically significant survival benefit from adding chemotherapy in terms of OS and PFS ($p = 0.05$ for PFS and 0.02 for OS). The patients treated with RT and chemotherapy had PFS-15 and OS-15 rates of 82.3% and 89.3% versus PFS-15 and OS-15 rates of 38.5% and 52.0% with RT alone.

We did not find a higher toxicity from the addition of chemotherapy compared to toxicity rates reported by in literature (12;13). By analyzing safety data, as expected, the main toxicities were neutropenia and thrombocytopenia and among all patients receiving chemotherapy we reported a grade ≥ 3 hematologic adverse events incidence rate of 42% compared to 16% reported in the group of patients who received RT alone and a negligible rate of grade ≥ 3 gastrointestinal effects (8% for grade 3 nausea). The events were reversible in all cases and only for 3 patients (13%) we recurred to the use of granulocytes- colony stimulating factors. None died for adverse events related to chemotherapy.

As in children, a possibility to reduce acute treatment-related toxicities also in adult patients is to decrease the dose of RT in patients receiving chemotherapy through the development of new radiation therapy technologies such as proton beam cranio-spinal irradiation. The always growing use of these new strategies in the next future could allow to obtain an increasing survival from the addition of chemotherapy to adjuvant radiotherapy with a better profile of gastrointestinal and hematologic safety (17).

Conclusions

A statistically significant benefit from addition of adjuvant chemotherapy in the management of medulloblastoma average-risk adult patients resulted from our study after a median follow up of 12.5 years. This benefit is considerable many years (15 or more) far from surgery since tumor relapses are often delayed in average-risk disease. Many questions remain open about timing and schedules of

chemotherapy and the possibility to reduce radiotherapy doses and, consequently, toxicities. Further research is needed to eventually standardize the role of chemotherapy for this rare group of patients.

Abbreviations

PFS
progression-free survival
OS
overall survival
CNS
central nervous system
MRI
magnetic resonance imaging
CSF
cerebro-spinal fluid
RT
radiotherapy
CT
chemotherapy

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare they have no competing interests.

Funding

No funding was received

Authors' contributions

EF and SM has made drafting the work; AM, AT, MM, CT, SB and AAB have revised the work critically for important intellectual content and has given final approval of the version to be published; EF, SM, AM, AT, MM, CT, SB have helped to draft and revise the manuscript; AAB has given substantial contributions to the conception of the work; all authors have given agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript. Neither author received any source of funding for this paper.

Aknowledgements

Not applicable

References

1. Peris-Bonet R, Martínez-García C, Lacour B, Petrovich S, Giner-Ripoll B, Navajas A, Steliarova-Foucher E. Childhoodcentral nervous system tumours–incidence and survival in Europe (1978-1997): report from Automated Childhood Cancer Information System project.Eur J Cancer. 2006 Sep;42(13):2064-80.
2. Smoll NR, Drummond KJ. The incidence of medulloblastomas and primitive neurectodermaltumours in adults and children.J ClinNeurosci. 2012 Nov;19(11):1541-4.
3. Brandes AA, Franceschi E, Tosoni A, Blatt V, Ermani M. Long-termresults of a prospective study on the treatment of medulloblastoma in adults.Cancer. 2007 Nov 1;110(9):2035-41.
4. Brandes AA, Franceschi E, Tosoni A, Reni M, Gatta G, Vecht C, Kortmann RD. Adultneuroectodermal tumors of posterior fossa (medulloblastoma) and of supratentorial sites (stPNET).Crit Rev Oncol Hematol. 2009 Aug;71(2):165-79. doi: 10.1016/j.critrevonc.2009.02.002. Epub 2009 Mar 19. Review.
5. D'Arco F, Culleton S., De Cocker L.J.L., Mankad K., Davila J., Tamrazi B. Current concepts in radiologic assessment of pediatric brain tumors during treatment, part 1. Pediatric Radiology, 2018 Jul 6.
6. Abacioglu U, Uzel O, Sengoz M, Turkan S, Ober A. Medulloblastoma in adults: treatment results and prognostic factors.Int J Radiat Oncol Biol Phys. 2002 Nov 1;54(3):855-60.
7. Packer RJ, GoldweinJ, Nicholson HS, Vezina LG, Allen JC, Ris MD, Muraszko K, Rorke LB, Wara WM, Cohen BH, Boyett JM. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study.JClinOncol. 1999 Jul;17(7):2127-36.
8. Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, Bayer L, LaFond D, Donahue BR, Marymont MH, Muraszko K, Langston J, Sposto R. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma.JClinOncol. 2006 Sep 1;24(25):4202-8.
9. Brandes AA, Ermani M, Amista P, Basso U, Vastola F, Gardiman M, Iuzzolino P, Turazzi S, Rotilio A, Volpin L, Mazza C, Sainati L, Ammannati F, Berti F. The treatment of adults with medulloblastoma: a

prospective study.Int J Radiat Oncol Biol Phys. 2003 Nov 1;57(3):755-61.

10. Padovani L, Sunyach MP, Perol D, Mercier C, Alapetite C, Haie-Meder C, Hoffstetter S, Muracciole X, Kerr C, Wagner JP, Lagrange JL, Maire JP, Cowen D, Frappaz D, Carrie C. Common strategy for adult and pediatric medulloblastoma: a multicenter series of 253 adults. Int J Radiat Oncol Biol Phys. 2007 Jun 1;68(2):433-40.
11. Greenberg H.S., Chamberlain M.C., Glantz M.J., and Wang S.. Adult medulloblastoma: Multiagent chemotherapy. Neuro-Oncology 3, 29–34, 2001
12. Friedrich C, von Bueren AO, von Hoff K, Kwiecien R, Pietsch T, Warmuth-Metz M, Hau P, Deinlein F, Kuehl J, Kortmann RD, Rutkowski S. Treatment of adultnonmetastatic medulloblastoma patients according to the paediatric HIT 2000 protocol: a prospective observational multicentre study.Eur J Cancer. 2013 Mar;49(4):893-903. doi: 10.1016/j.ejca.2012.10.006. Epub 2012 Nov 19.
13. Beier D, Proescholdt M, Reinert C, Pietsch T, Jones DTW, Pfister SM, Hattingen E, Seidel C, Dirven L, Luerding R, Reijneveld J, Warmuth-Metz M, Bonsanto M, Bremer M, Combs SE, Rieken S, Herrlinger U, Kuntze H, Mayer-Steinacker R, Moskopp D, Schneider T, Beringer A, Schlegel U, Stummer W, Welker H, Weyerbrock A, Paulsen F, Rutkowski S, Weller M, Wick W, Kortmann RD, Bogdahn U, Hau P. Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). Neuro Oncol. 2018 Feb 19;20(3):400-410. doi: 10.1093/neuonc/nox155.
14. Kortmann RD, Kühl J, Timmermann B, Mittler U, Urban C, Budach V, Richter E, Willich N, Flentje M, Berthold F, Slavc I, Wolff J, Meisner C, Wiestler O, Sörensen N, Warmuth-Metz M, Bamberg M. Postoperativeneoadjuvantchemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91.Int J Radiat Oncol Biol Phys. 2000 Jan 15;46(2):269-79.
15. Tarbell NJ, Friedman H, Polkinghorn WR, Yock T, Zhou T, Chen Z, Burger P, Barnes P, Kun L. High-riskmedulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031).J ClinOncol. 2013 Aug 10;31(23):2936-41. doi: 10.1200/JCO.2012.43.9984. Epub 2013 Jul 15.
16. Franceschi E, Bartolotti M, Paccapelo A, Marucci G, Agati R, Volpin L, Danieli D, Ghimenton C, Gardiman MP, Sturiale C, Poggi R, Mascarin M, Balestrini D, Masotto B, Brandes AA. Adjuvant chemotherapy in adult medulloblastoma: is it an option for average-risk patients?J Neurooncol. 2016 Jun;128(2):235-40.
17. Brown AP, Barney CL, Grosshans DR, McAleer MF, de Groot JF, Puduvalli VK, Tucker SL, Crawford CN, Khan M, Khatua S, Gilbert MR, Brown PD, Mahajan A. Protonbeamcraniospinal irradiation reduces acute toxicity for adults with medulloblastoma.Int J Radiat Oncol Biol Phys. 2013 Jun 1;86(2):277-84.

Tables

Due to technical limitations, Tables 1-2 are provided in the Supplementary Files section.

Figures

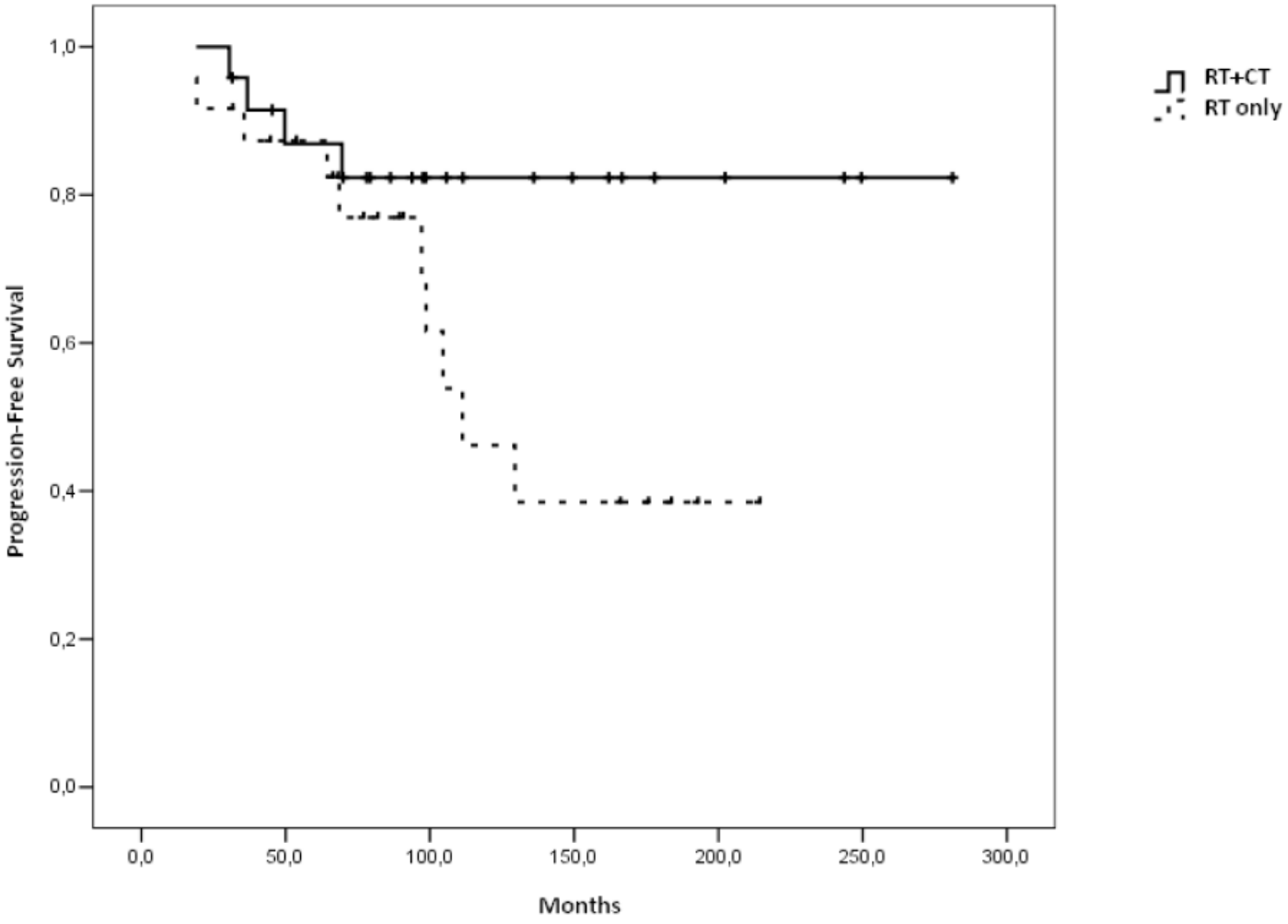

Figure 1

PFS according to treatment

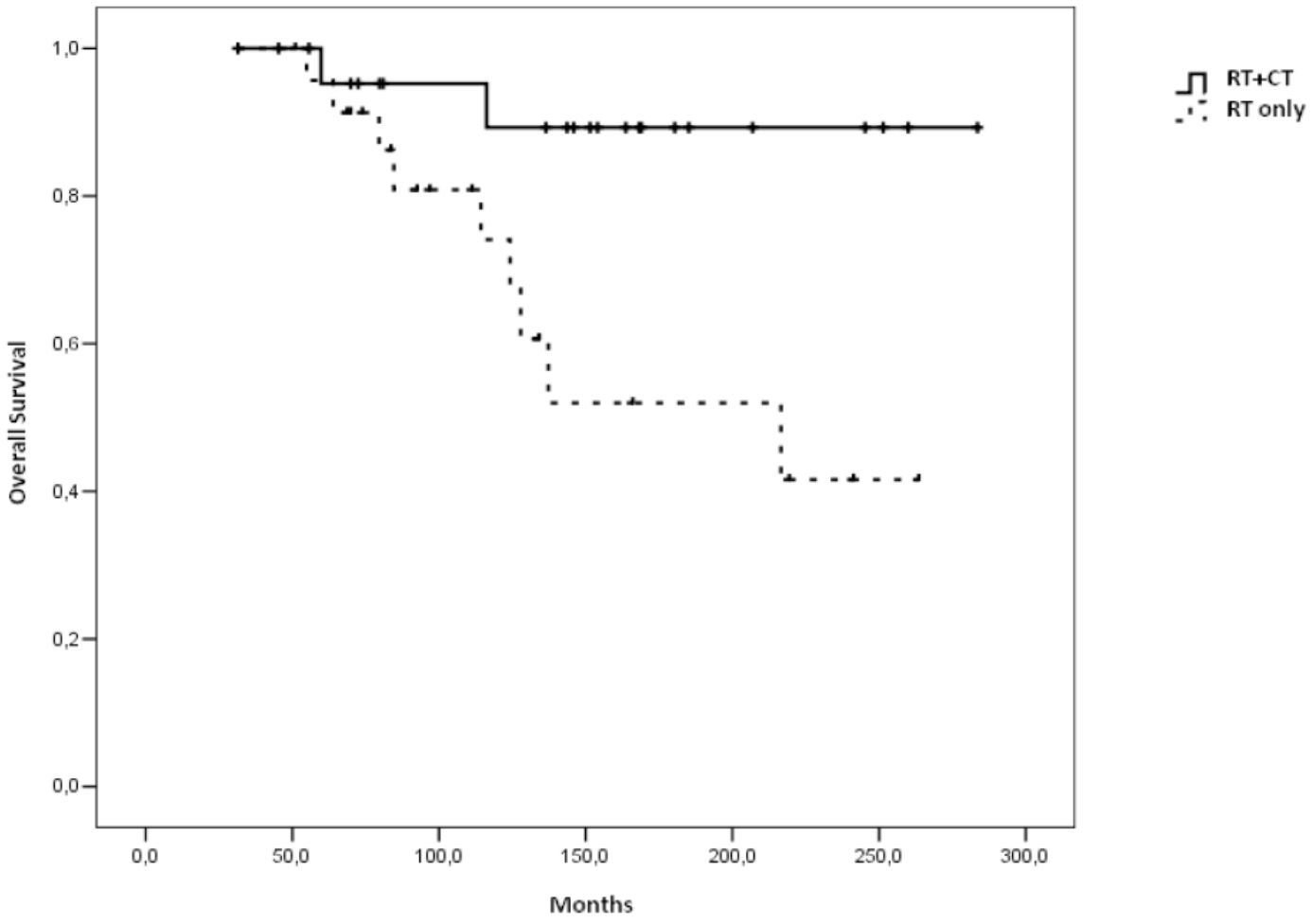

Figure 2

OS according to treatment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf
- asco2019.pdf
- medullo2016.pdf