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Original Research Article

MacDonald versus MAGIC treatment protocols for gastric cancer: age as a decision factor

André Figueiredo*, Diogo Delgado, Helena Luna Pais, Maria Filomena de Pina

Department of Radiation Oncology, North Lisbon University Hospital Center, EPE, Lisbon, Portugal

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***Correspondence:**
Dr. André Figueiredo,
E-mail: andrepinheirofigueiredo@gmail.com

ABSTRACT

Background: A multimodality approach is the standard of care in the treatment of locally advanced non-metastatic gastric cancer. However, it lacks studies that compares the adjuvant chemoradiotherapy strategy of the landmark MacDonald clinical trial with the perioperative chemotherapy strategy of the landmark MAGIC clinical trial.
Methods: Retrospective study of patients with gastric cancer stage IB-III treated at a single cancer center between 2010 and 2013 with MacDonald or MAGIC treatment protocols.
Results: Sixty-two patients were identified (38 patients in the MacDonald protocol and 24 in the MAGIC protocol), with a mean age of 68 years (range: 39-84). At a median follow-up of 37 months, the DFS survival at 12 and 36 months of the patients in the MacDonald protocol was 83.5% and 61.1% versus 79.2% and 49.7% in the MAGIC protocol, respectively (p=0.319). The overall survival at 12 and 36 months of the patients in the MacDonald protocol was 89.5% and 65.8% versus 83.3% and 54.2% in the MAGIC protocol, respectively (p=0.168). At multivariate analysis, the risk of death was significantly superior in older patients undergoing the MAGIC protocol (p=0.02), but not the MacDonald protocol (p=0.627). The differences in toxicity between the two protocols were not statistically different.
Conclusions: This result suggest that patient age is a factor to consider when choosing between the MacDonald or MAGIC protocols. However, the limitations inherent to a retrospective study of small sample size must be accounted for.

Keywords: Gastric cancer, MacDonald protocol, MAGIC protocol

INTRODUCTION

Besides the steadily reduction in incidence over the last 50 years, gastric cancer remains the 5th most common new diagnosis of cancer in the world1. Also, it remains one of the deadliest: according to GLOBOCAN's last publication, it is the third cause of cancer mortality, tied with liver cancer, just behind lung and colorectal cancers.[2] The survival rates reported are particularly distinct between countries, however there is a trend towards better survival rates in the last years reflecting the earlier diagnosis and better treatment protocols.[1] For pre-metastatic diagnosis, the 5-year overall survival (OS) reported is 67%.[1] That includes the IA and IB stage disease with reported 5-year OS of 94% and 88% respectively, until the stage IIIC with a much worse reported 5-year OS of 18%.[1]

The multimodality treatment is the standard of care in stage IB to III gastric cancer.[3] MacDonald et al, published in 2001 the landmark trial that showed an OS benefit in patients with gastroesophageal junction or gastric cancer treated with chemoradiotherapy after surgery compared to surgery alone (median OS of 36 months versus 27 months respectively, HR for death in surgery alone group = 1.35, 95% CI = 1.09-1.66, p=0,005).[4] Cunningham et al, published in 2006 the MAGIC trial that also showed an OS benefit in these patients but with a perioperative

chemotherapy approach (HR for death in perioperative group = 0.75, 95% CI = 0.6-0.93, p=0.009).[5] Since then, the multimodality treatment in these stages continues to be the standard of care, even though new chemotherapy protocols emerged.[3] The uncertainty of which treatment strategy (perioperative chemotherapy or adjuvant chemoradiotherapy) is superior still exists for some patients, even with the results of more recent clinical trials that compared chemotherapy to chemoradiotherapy in resectable gastric cancer.[6]

This study pretends to compare the outcomes of toxicity, disease-free survival (DFS) and OS of patients treated with MAGIC protocol versus MacDonald protocol in a university hospital center.

METHODS

All the patients treated at this hospital center with gastric cancer between 2010 and 2013 were identified using an internal database. This time length was chosen to have at least the possibility of a 5-year follow-up to all patients. After that, data was limited to the patients that were pathologic staged as IB to IIIC (by the 7th AJCC Staging System) and were treated with the MAGIC or MacDonald protocols. In these protocols, patients of both treatment groups underwent gastric surgery. In the MAGIC protocol the perioperative chemotherapy was divided in three cycles preoperatively and three cycles postoperatively, each one consisted of epirubicin, cisplatin and fluorouracil. In the MacDonald protocol the patients were submitted to a postoperative combination of fluorouracil plus leucovorin and locoregional radiation therapy. The prescribed radiation dose of 45 Gy was delivered in 25 fractions, five days per week, to the tumor bed and regional nodes. Patients were treated with a 3D conformal radiotherapy technique using high energy photons.

The following data was collected: sex, age, history of another neoplasm (before or after the diagnosis of gastric cancer, but not concomitant), date of diagnosis, disease localization (gastroesophageal junction (GEJ), gastric cardia, antrum, body or pylorus, or multiple localizations), histology (adenocarcinoma, signet ring cell carcinoma or mixed-type), type of surgery (subtotal or total gastrectomy with/without D2 lymphadenectomy), radiotherapy prescribed dose, type and grade of toxicity during treatment, completeness of the treatment protocol, date of the last follow-up and date of recurrence and/or death if applicable. Both groups were compared for all the categories referred before with the chi-square test for categorical variables and the t-test for continuous variables. DFS survival was calculated from diagnosis to the first event (local recurrence or progression, distant failure or death) and OS was calculated from diagnosis to death. The death event could be from any cause and no cause differentiation was made. Event-free patients were censored on the date of the last follow-up. The Kaplan-Meyer method was used for the construction of DFS and OS curves. These outcomes were compared in both groups using the log-rank test. A multivariate Cox regression analysis was performed for each group of treatment. Statistical significance was defined as $p<0.05$.

All the statistic calculations were carried out by using the tools provided by IBM SPSS Statistics version 24.

RESULTS

Sixty-two patients were identified (38 patients in the MacDonald protocol and 24 in the MAGIC protocol), with a median age of 68 years (range: 39-84). Both groups revealed slight male predilection. The main disease location was gastric antrum in the MacDonald protocol and gastric body in the MAGIC protocol. The most common histology type found in both groups was adenocarcinoma. In association with total or subtotal gastrectomy 19(30.6%) patients had D2 lymphadenectomy (8 patients in the MacDonald protocol and 11 patients in the MAGIC protocol, p= 0.09). Forty-six (74.2%) patients had (y)pT3/T4 disease versus (y)pT1/T2 disease. Thirty-four (89.5%) patients in the MacDonald protocol and 13(54.2%) patients in the MAGIC protocol had (y)pN+ disease (p=0.003) (Table 1).

No statistically different baseline characteristics were found between the two treatment groups in terms of sex (p=0.546), age (p=0.77), history of another neoplasm (p=0.214), location of the disease (p=0.445), histology type (p=0.505), grade (p=0.213) and number of patients who completed the treatment protocol (p=0.111). The number of patients submitted to D2 lymphadenectomy was significantly superior in the MAGIC treatment group versus the MacDonald treatment group. The pathological lymph node stage was also significantly different between the two treatment regimens, with more pathological positive lymph nodes in patients submitted to the MacDonald protocol versus the MAGIC protocol. The prescribed cycles of chemotherapy were completed in 86,2% of the patients in the MacDonald protocol versus 66,7% in the MAGIC protocol, a difference not statistically different (p=0.111).

No differences in toxicity (hematologic, gastrointestinal or other) were observed between the two protocols. However, there was a trend towards more gastrointestinal (GI) toxicity with the MacDonald protocol versus the MAGIC protocol (23,7% versus 4,2% of patients had G3/G4 GI toxicity, p=0,073) (Table 2).

At a median follow-up of 37 months, the DFS survival at 12 and 36 months of the patients in the MacDonald protocol was 83.5% and 61.1% versus 79.2% and 49.7% in the MAGIC protocol, respectively (log-rank p=0.319) (Figure 1). The overall survival at 12 and 36 months of the patients in the MacDonald protocol was 89.5% and 65.8% versus 83.3% and 54.2% in the MAGIC protocol, respectively (log-rank p=0.168) (Figure 2).

Table 1: Baseline characteristics of both treatment groups.

	MacDonald (n=38)	MAGIC (n= 24)	Both (n= 62)
Median Age, yr (range) (p=0.77)	67(51-81)	68(39-84)	68(39-84)
Men (p=0.546)	23(60,5)	15(62,5)	38(61,3)
Disease Location (p=0.445)			
GEJ	1(2.6)	1 (4.2)	2(3.2)
Cardia	1(2,6)	0 (0)	1(1.6)
Antrum	19(50)	7 (29.2)	26(41.9)
Body	11(28.9)	11 (45.8)	22(35.5)
Pylorus	3(7.9)	1(4.2)	4(6.5)
Multiple Locations	3 (7.9)	4 (16.7)	7 (11.3)
Histology Type (p=0.505)			
Adenocarcinoma	34 (89.5)	23(95.8)	57(91.9)
Signet ring cell	2(5.3)	1(4.2)	3(4.8)
Mixed-type	2 (5.3)	0(0)	2(3.2)
Type of surgery (p= 0.062 for all type of surgeries and p=0.09 for D2 lymphadenectomy)			
Total gastrectomy	25(65.8)	17(70.9)	42(67.7)
Subtotal gastrectomy	13(34.2)	4(16.7)	17(27.4)
D2 lymphadenectomy**	8(21.1)	11(45.9)	19(30.6)
Pathologic stage (p=0.687 for pT stage and p=0.003 for pN stage)			
(y)pT1/T2***	10(26.3)	5(20.8)	15(24.2)
(y)pT3/T4	28(73.7)	18(75)	46(74.2)
(y)pN0	4(10.5)	10(41.7)	14(22.6)
(y)pN+	34(89.5)	13(54.2)	47(75.8)

*Data are expressed as No. (%) of patients (exception to age).
** in association with total or subtotal gastrectomy.
*** 3 patients ypT0.

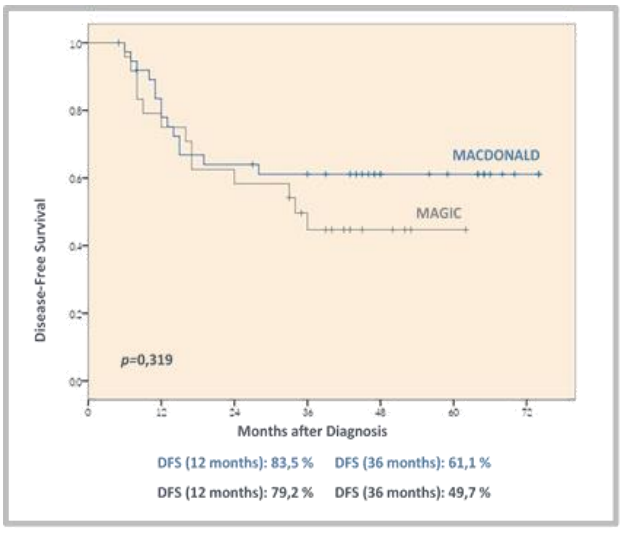

Figure 1: DFS curves of both treatment groups.

For multivariate analysis, it was explored if sex, pathological stage (pT and pN) or age were prognostic of DFS and overall survival for each treatment group. The risk of death was significantly superior in older patients undergoing the MAGIC protocol (HR = 1.07, 95% CI = 1,01-1,13; p=0.02), but not the MacDonald protocol (HR = 1.05, 95% CI = 0,98 – 1,13; p=0.175). Age was also a prognostic factor for recurrence in patients undergoing the MAGIC protocol (HR=1,06, 95% CI=1,005-1,119; p= 0,032),but not the MacDonald protocol (HR=1,05, 95% CI =0,98 - 1,4; p=0,18) (Table 3).

Table 2: Toxicity of both treatment groups.

	MacDonald (n=38)	MAGIC (n= 24)	Both (n=62)
Completed protocol** (p=0.111)	25 (65.8)	16 (66.7)	41(66.1)
G3/ G4 toxicity			
Hematologic	11 (28.9)	9 (37.5)	20(32.3)
Gastrointestinal	9 (23.7)	1 (4.2)	10(16.1)
Other	9 (23.7)	6 (25)	15(24.2)

*Data are expressed as No. (%) of patients.
** 9 patients without information about completeness of the protocol.
** in accordance with National Cancer Institute Common Toxicity Criteria.

Table 3: Multivariate analysis of prognostic factors in both treatment groups.

	MacDonald	MAGIC
Multivariate analysis for DFS		
Age	HR 1,05 (0,98–1,4) p=0,18	HR 1,06 (1,005–1,119) p=0,032
Sex	HR 1,08 (0,338–3,44) p=0,9	HR 0,71 (0,21–2,42) p=0,59
Stage pT	p=0,95	p=0,96
Stage pN	HR 0,66 (0,139–3,14) p=0,6	HR 1,55 (0,4–6) p=0,53
Multivariate analysis for OS		
Age	HR 1,05 (0,98–1,13) p=0,175	HR 1,07 (1,01–1,13) p=0,02
Sex	HR 1,46 (0,46–4,7) p=0,52	HR 0,66 (0,193–2,27) p=0,51
Stage pT	p=0.96	p=0,96
Stage pN	HR 0,59 (0,12–2,9) p=0,51	HR 1,58 (0,41–6,1) p=0,51

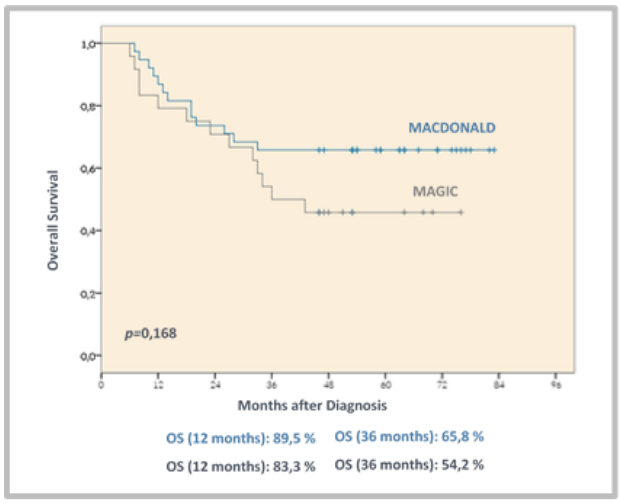

Figure 2: OS curves of both treatment groups.

DISCUSSION

Since the publication of the results of the landmark clinical trials responsible for the MacDonald and MAGIC treatment regimens in 2001 and 2006 respectively, the standard of care in non-metastatic locally advanced gastric cancer has been a multimodality treatment.[3] Surgery continues to be the cornerstone, but chemotherapy or chemoradiotherapy is critical to improve DFS and OS.[3]

However, no randomized clinical trials comparing these two treatment regimens have been published. Jayanathan et al, published in 2019 a retrospective study using the National Cancer Database (of the United States) and explored 9243 patients with gastric cancer staged IB-III from 2005 to 20147. They found that the majority received a multimodality treatment (57% of patients), with a clear OS advantage compared to patients submitted to surgery alone (p <0.0001).[7] They also noted that the use of multimodality therapy had a dramatic rise between the time length of the study, particularly perioperative chemotherapy regimen (7.5% in 2006 to 46% in 2013).[7] A comparison using a propensity matched method between perioperative chemotherapy and adjuvant chemoradiotherapy didn't find a statistically difference in OS7. It was noted that academic centers were significantly more likely to treat the patients with perioperative chemotherapy.[7] The authors suggested that the reason could be the higher toxicity associated with this protocol and so large volume centers were more comfortable with managing it.[7]

Cheng et al, published in 2015 a prospective database of 150 patients with gastric cancer who had resection with curative intent between 2000 and 2013, and divided them in two cohorts.[8] The early cohort included patients treated from 2000 to 2006 and the late cohort included patients treated from 2007 to 2013.[8] They found that patients treated with perioperative chemotherapy increased from 3.6% in the early cohort to 34% in the late cohort (p<0.001).[8] The use of adjuvant chemoradiotherapy did not differ between the two cohorts (50% versus 38% respectively, p=0.21).[8] Of note, the median OS was 24.9 months for the early cohort while the median OS for the late cohort was not reached at the time of publication (p=0.01)8. A more extensive lymph node dissection, a rise in perioperative chemotherapy regimen and more variety of chemoradiotherapy regimens were the possible reasons to the improved OS according to the authors8. Unfortunately, no direct comparison of DFS and OS between the two treatment regimens was made. The 4-year OS in the early cohort was 32.6% and in the late cohort was 68.8%.[8] This 3-year OS was 61.1% in MacDonald and 49.7% in MAGIC treatment groups, so author can assume that this outcomes are more proximal to the late cohort group versus the early cohort group. This is expected given the multimodality treatment approach used in all this patients. This 3 year DFS and 3 year OS outcomes compare favorably to the MacDonald and the MAGIC reported survival outcomes (3-year DFS of 61.1% versus 48% and 49.7% versus 40%; 3-year OS of 65.8% versus 50% and 54.2% versus 45%, respectively).

The main criticism made to the MacDonald clinical trial was the poor surgery approach with only 10% of the

patients submitted to a D2 lymphadenectomy and 54% with only a D0 nodal dissection. In this study, 30.6% of the patients undergone a D2 lymphadenectomy, however with a significant difference between the patients in MAGIC versus MacDonald treatment protocols (45.9% versus 21.1% respectively, p=0.009). This should always be taken into account when interpreting the OS results in this cohort of patients. The proportion of the patients who underwent D2 lymphadenectomy in this MAGIC treatment group is similar with the original MAGIC clinical trial (45.9% versus 42.5% respectively).

The pathological lymph node stage was also significantly different between the two treatment regimens, with more pathological positive lymph nodes in the group submitted to MacDonald protocol versus the MAGIC protocol, an expected result given the neoadjuvant chemotherapy in the MAGIC protocol.

Given the absence of difference in DFS and OS outcomes between the MacDonald and MAGIC protocols, author explored the possibility of some patients benefiting more with one protocol versus the other. For that purpose, author used a multivariate analysis for each treatment group with four variables: sex, age, stage pT and stage pN. The only factor with a statistically significant impact in DFS and OS outcomes was age in the MAGIC treatment group (p=0.032 and p=0.02 respectively) but not in the MacDonald treatment group (p=0.18 and p=0.175 respectively). This result raises the question if in older patients the perioperative chemotherapy protocol with ECF is particularly toxic. In the MAGIC original clinical trial, no subgroup analysis was reported, however it should be noted that only 42% of the patients completed the entire protocol. Early disease progression, patient request and postoperative complications were highlighted by the authors as the main reasons for patients who didn't initiate the adjuvant protocol. Given the impact that age had in DFS and OS on this cohort of patients who received the MAGIC treatment regimen, one explanation could be the particularly high postoperative complications after neoadjuvant chemotherapy in more fragile older patients. It should be referred that the median age of the patients in the MacDonald clinical trial (60 years (range: 25-87)) and the MAGIC clinical trial (62 years (range: 29-85)) is roughly similar to this cohort of patients (68 years (range: 39-84)).

In this patients, the reported G3/4 toxicity (hematologic, GI or other) was not statistically different between the MacDonald and MAGIC treatment protocols. It should be noted that the proportion of patients in the MacDonald protocol with G3/4 hematologic or GI toxicity in this study compares favorably with the reported toxicity in the original MacDonald clinical trial (28.9% and 23.7% versus 54% and 33% respectively). This result must be interpreted with caution given the more controlled approach of a clinical trial; whose adverse events reports are likely better. No comparison can be made with the original MAGIC clinical trial given the report divided by preoperative and postoperative toxicity and with different subcategories within the hematologic and GI toxicity. In this study, there was a trend towards more GI toxicity with the MacDonald protocol versus MAGIC protocol, a result that was expected given the radiation dose received by the GI tract in MacDonald protocol.

The ECF regimen is no longer the standard of care in the treatment of gastric cancer. In 2017, Al-Batran et al, published the first results of FLOT4 trial that showed an OS benefit for patients treated with docetaxel-based triplet FLOT compared to the ECF/ECX chemotherapy protocol used in the MAGIC trial (median OS of 50 months versus 35 months respectively, HR for death in FLOT group = 0.77, 95% IC = 0.63-0.94, p=0.012).[9] The validity of this results compared to this new chemotherapy regimen has to be confirmed.

Two other important clinical trials in gastric cancer have to be mentioned given the comparison made between the chemotherapy alone versus chemoradiotherapy treatment approaches with results questioning the benefit of radiotherapy.[6]

Lee et al, published the ARTIST trial in 2012 comparing adjuvant chemotherapy alone to adjuvant chemoradiotherapy (also with chemotherapy before and after in the combined treatment) and showed that the addiction of chemoradiotherapy in patients submitted to curative gastric cancer surgery with D2 lymphadenectomy did not provide benefit in locoregional control of the disease.[10] However, the subgroup analysis did find a statistically significant prolongation in DFS survival in patients with positive pathologic lymph node gastric cancer submitted to chemoradiotherapy versus chemotherapy alone.[10] This analysis gave rise to the ARTIST-II trial that compare chemotherapy alone (two regimens) versus chemoradiotherapy in lymph node positive gastric cancer patients.[11]

The final results are pending. Cats et al, published in 2018 the CRITICS trial that compared perioperative chemotherapy to neoadjuvant chemotherapy with adjuvant chemoradiotherapy.[12] There was no statistically difference in OS between the two groups (median OS of 43 months versus 37 months respectively, p=0.9).[12]

CONCLUSION

In conclusion, author highlight that our results suggest that age could be a factor to consider when choosing between the MAGIC or the MacDonald treatment protocols. However, the limitations inherent to a retrospective study of small sample size must be accounted for. The validity of our results when using other chemotherapy regimens must be confirmed and could be the rational for the design of a new study in gastric cancer.

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