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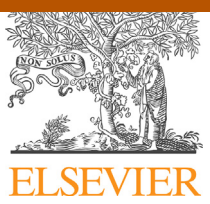

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Original Article

Assessment of prognosis in patients with stage II colon cancer

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ABSTRACT

Pathologic staging is currently the most important prognostic factor in colon cancer, although individually this procedure does not provide a complete clinical outcome.

This study aimed to determine the disease-specific survival of patients with colon cancer treated in the Braga Hospital from January 2005 to December 2013, according to the American Joint Committee on Cancer, 6th edition, and the disease-free survival and disease-specific survival of high- and low-risk stage II patients, whether in use, or not, of adjuvant chemotherapy.

We obtained a total sample of 578 patients, with 145 and 65 high- and low-risk stage II patients, respectively. We observed a 5-year disease-specific survival rate of 93%, 27.4% and 75% for stage IIA, IIB and IIIA patients, respectively, where IIIA and IIB present statistically significant differences ($p = 0.001$). In high-risk stage II patients, disease-free survival ($p = 0.107$) and disease-specific survival ($p = 0.037$) were higher in the group submitted to chemotherapy. In low- risk patients, disease-free survival was higher in the group submitted to chemotherapy ($p = 0.494$), while disease-specific survival was lower ($p = 0.426$).

The differences observed between stage IIB and IIIA survival can be explained by the consensual use of adjuvant chemotherapy in stage IIIA, and by its controversial use in stage IIB. Adjuvant chemotherapy showed to be effective only in high-risk stage II patients in terms of disease-specific survival.

In the future, other markers, namely molecular ones, may be used to stratify the risk of stage II patients and determine who will benefit from adjuvant chemotherapy.

Avaliação o prognóstico de pacientes com cancer de colon no estadio II

Palavras-chave:
Câncer de cólon
Estadio II de alto risco e baixo risco
Sobrevivência livre de doença

RESUMO

O estadiamento patológico é, atualmente, o fator de prognóstico mais importante do câncer de cólon, embora individualmente não preveja totalmente o resultado clínico.

Neste estudo, pretendeu-se determinar a sobrevivência para uma doença específica (SDE) dos pacientes com câncer de cólon tratados no Hospital de Braga entre janeiro de 2005 e

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Sobrevivência para uma doença específica

dezembro de 2013, de acordo com a 6ª edição da American Joint Committee on Cancer e a Sobrevivência Livre de Doença (SLD) e SDE dos doentes em estadio II, classificados em alto e baixo risco, de acordo com a realização ou não de quimioterapia adjuvante.

Obtivemos uma amostra total de 578 pacientes, dos quais uma parcela pertencia ao estadio II de alto ou de baixo risco (145 e 65 pacientes, respetivamente). Observamos SDE a 5 anos de: 93%, 27,4% e 75% para os estadios IIA, IIB e IIIA, respetivamente; IIIA e IIB apresentaram diferenças significativas (p = 0,001). SLD (p = 0,107) e SDE (p = 0,037) para o estadio II de alto risco foram superiores no grupo tratado com quimioterapia. Nos doentes de baixo risco, SLD foi superior no grupo tratado com quimioterapia (p = 0,494), enquanto que SDE foi inferior (p = 0,426).

As diferenças de sobrevivência observadas para os estadios IIB e IIIA podem se dever ao uso controverso da quimioterapia em IIB e ao uso consensual em IIIA. O uso da quimioterapia adjuvante demonstrou ser efetivo nos doentes em estadio II de alto risco em termos de SDE.

Futuramente, outros marcadores, nomeadamente moleculares, poderão vir a ser utilizados para estratificar o risco do estadio II e definir quem se beneficiará com o tratamento adjuvante.

Introduction

The incidence of neoplasms and the associated mortality have been increasing worldwide.[1] In 2012, colorectal cancer (CRC) was rated third place among neoplasias with the highest incidence (1.4 million cases, 9.7%) and was rated 4th place in terms of mortality (8.5%) worldwide.[2] In Portugal, CRC is rated 2nd place among neoplasias with highest incidence and mortality in both men and women, with an incidence and mortality of 14.8% and 15.7% in men and 14.1% and 15.9% in women, respectively.[2] In 2008, in northern Portugal, CRC was the second most frequent neoplasia, both in women (15.1%) and men (18.7%).[3]

Currently, pathologic staging is the most important prognostic factor, although individually this procedure cannot fully predict the clinical outcome,[4–6] and the staging system most often used is the Tumor-Node-Metastasis (TNM) system of the American Joint Committee on Cancer (AJCC). As the stage progresses from I to IV, the overall five-year survival falls from values greater than 90% (stage I) to less than 10% (stage IV). Stages II and III have overall survivals of 70–85% and 25–80%, respectively.[7]

In recent decades, the prognosis has been improving, thanks to factors such as an earlier diagnosis and staging and treatment advances.[8–10] More recently, the 6th edition of AJCC[11] was revised, and its 7th edition (2010) is currently in use.[12]

Thus, staging procedures are useful for proposing the prognosis; however, T3-4N0 (stage II) patients have a worse Disease-Specific Survival (DSS) (87.5%, 79.6%, 58.4%) versus T1-2N1a (stage III) patients (90.7%).[13] This suggests that other factors contribute to the prognosis of the patients, namely, the presence of perforation or intestinal obstruction at the time of diagnosis, preoperative increase in carcinoembryonic antigen, low histological differentiation, presence of lymphovascular and perineural invasion, and resection of less than 12 lymph nodes together with the surgical specimen.[14,15]

The higher DSS of T1-2N1a patients with respect to stage II can also be justified by the fact that, for stage III patients, the benefits of adjuvant chemotherapy are established; on the other hand, the use of this therapy still remains controversial for stage II patients.[16,17] This controversy is well documented in a literature review conducted by André et al.,[18] in which several studies document absence of benefit with adjuvant chemotherapy for overall and disease-free survival in stage II patients, including the study International Multicentre Pooled Analysis of B2 of Cancer Trials (IMPACT B2),[19] the meta-analysis by Figueiredo et al.[20] and a meta-analysis published by the Mayo Clinic.[21] On the other hand, the analysis of the National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies (NSABP) (21), a Japanese meta-analysis[22] and the study Quick and Simple and Reliable Study (QUASAR)[23] found benefits in its use, and NSABP noted that adjuvant chemotherapy reduces extensively the risk of recurrence.[21] The group Adjuvant Rectal Cancer Endpoints (ACCENT) also found benefit with the use of adjuvant chemotherapy in stage II patients, in terms of survival.[24]

According to the National Cancer Institute, the decision to introduce adjuvant chemotherapy for stage II patients must be made individually; presently, this procedure is not suitable for most patients, unless they are included in clinical trials.[25]

According to the European Consensus of 2014 for the European Registration of Cancer Care (EURECCA), one should consider the use of adjuvant chemotherapy in high-risk stage II patients, including those with T4 tumors, with less than 10 lymph nodes examined, presenting venous and lymphatic invasion, with poor tumor differentiation, and with tumor perforation.[26] The same criteria are used by the American Society of Clinical Oncology (ASCO) to identify stage II patients who should undergo adjuvant chemotherapy, with the exception that ASCO consider a minimum of 12 nodes instead of those 10 nodes mentioned in the EURECCA consensus, imposing also the presence of bowel obstruction as one of the selection criteria.[27]

The literature is very controversial on the role of adjuvant chemotherapy in stage II patients; thus, the aim of this study is to carry out an assessment on this topic in patients treated at the Braga Hospital.

Materials and methods

The target population for the study consisted of patients with colon adenocarcinoma treated at the Braga Hospital between January 1, 2005, and December 31, 2013. A sample of convenience, consisting of 578 patients, was elaborated based on the following inclusion/exclusion criteria.

Inclusion criteria: Postoperative histological diagnosis of colon adenocarcinoma in patients who underwent curative surgical resection at the Braga Hospital between January 1, 2005, and December 31, 2013.

Exclusion criteria: Patients with a different histological diagnosis from the mentioned above; patients with rectal adenocarcinoma; patients who died in the first 30 days after surgery; patients who underwent primary therapy; patients with a personal history of CRC and hereditary syndromes.

Methodology

A prospective analysis of the Coloproctology Unit database at the Braga Hospital was held, consisting of clinical, pathological and follow-up data. Subsequently, stage II patients were divided into two groups: of low-and high-risk, based on criteria defined by the EURECCA consensus.[26]

This project was approved by the Ethics Committee for Health and by the Ethics Subcommittee for Life and Health Sciences of the Braga Hospital.

Statistical analysis

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) software, version 19.0 (SPSS Inc., Chicago, IL, USA).

For the total sample of patients, a descriptive analysis of variables was performed. Next, Kaplan–Meier curves for DSS and for the different stages of AJCC (6th edition) were obtained. The Log-Rank test (Mantel–Cox), with a significance set in 0.05, was applied to detect differences of DSS between groups. Five-year DSS was determined for all groups.

Kaplan–Meier curves for DFS and DSS were obtained for high- and low-risk stage II patients, according to the use or non-use of adjuvant chemotherapy.

The Log-Rank test (Mantel–Cox), with a significance set in 0.05, was applied to detect differences of DSS and DFS among the group treated with adjuvant chemotherapy versus non-treated group. Five-year DSS and DFS were determined for all groups.

DFS is defined as the period from surgery to recurrence of disease, and DSS as the period from surgery until the patient's died from the disease.

Results

Sample characterization

The study population consists of 578 individuals; 61.9% ($n = 358$) males and 38.1% ($n = 220$) females. The mean age at the time of surgery was 67.9 years.

As regards to the pathological staging, the study population had the following characteristics: 47.8% ($n = 276$) had nodal metastases and 14.4% ($n = 83$) were already with distant metastases.

As for the administration of adjuvant chemotherapy, this procedure was performed in 54.7% ($n = 316$) of patients, while 34.4% ($n = 199$) were not treated. During follow-up, 75.8% ($n = 375$) showed no recurrence of the disease; on the other hand, in 18.4% ($n = 91$) there was a recurrence. Overall, 19.9% ($n = 115$) died from the disease.

DSS analysis, according to AJCC (6th edition)

The mean DSS was calculated for the different stages, as follows: Stage I, 113.1 months (95% confidence interval [CI]: 109.5–116.7); stage IIA, 107.2 months (95% CI: 103.3–111.1); stage IIB, 46.4 months (95% CI: 17.9–74.9); stage IIIA, 93.8 months (95% CI: 67.9–119.6); stage IIIB, 89.7 months (95% CI: 81.2–98.2); stage IIIC, 63.3 months (95% CI: 48.5–78.1); and stage IV, 43.7 months (95% CI: 33.3–54.1). The mean DSS of this sample is 90.6 months (95% CI: 86.7–94.5). In paired comparisons between stages, statistically significant differences for DSS have been found in most cases, where the Log-Rank test obtained a p-value lower than 0.05, except between stages I and IIA (Log-Rank = 2.896; $p = 0089$); I and IIIA (Log-Rank = 3.658; $p = 0.056$); IIA and IIIA (Log-Rank = 0.109; $p = 0741$); IIB and IIIC (Log-Rank = 1.232; $p = 0.267$); IIB and IV (Log-Rank = 0.036; $p = 0.850$); and IIIA and IIIB (Log-Rank = 1.749; $p = 0.186$).

With regard to the five-year DSS by stage, we observed 100% for stage I; 93% (95% CI: 88.5–97.5%) for stage IIA; 27.4% (95% CI: 0–59.2%) for stage IIB; 75% (95% CI: 32.5–100%) for stage IIIA; 72.5% (95% CI: 62.3–82.7%) for stage IIIB; 51.1% (95% CI: 33.9–68.3%) for stage IIIC; and 28.3% (95% CI: 16.3–40.2%) for stage IV. The five-year DSS sample is 75.4% (95% CI: 71.1–79.7%). The survival curves are shown in Fig. 1.

Low-risk stage II patients' group assessment

The low-risk group consisted of 65 individuals, 60% ($n = 39$) male and 40% ($n = 26$) female. The mean age at diagnosis was 69.9 years.

As for the administration of adjuvant chemotherapy, this procedure was performed in 44.6% ($n = 29$) of patients, while 40% ($n = 26$) were not thus treated.

During the follow-up, 13.8% ($n = 9$) presented recurrence of the disease and 3.1% ($n = 2$) died from the disease. All patients who died belonged to the group that underwent adjuvant chemotherapy.

We compared the prognosis for low-risk stage II patients who underwent adjuvant chemotherapy versus those not thus treated. The mean DFS of low-risk stage II group was 84.2 months (95% CI: 73–95.4). The mean DFS for the low-risk group

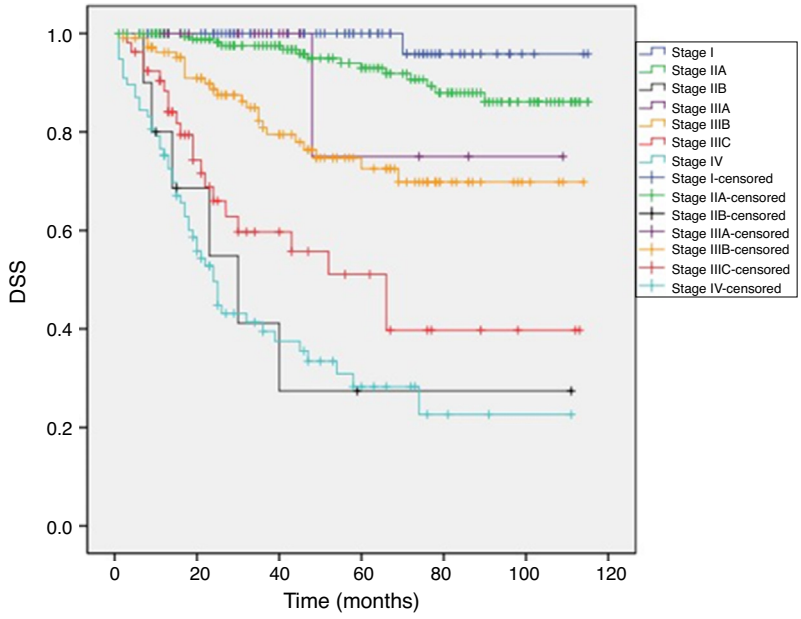

Fig. 1 – DSS for each stage of AJCC (6th edition).

who underwent adjuvant chemotherapy was 82.4 months (95% CI: 68.1–96.7), and for the group not thus treated, the mean DFS was 59.2 months (95% CI: 54.1–64.3). The DFS differences between the two groups are not statistically significant (Log-Rank = 0.468; $p = 0.494$).

The mean five-year DFS for the low-risk group was 71.3% (95% CI: 52.1–90.5%); for the group that underwent chemotherapy, the mean five-year DFS was 71.8% (95% CI: 51.6–92%) versus 63.8% (95% CI: 12.4–100%) for the group not thus treated. The survival curves are shown in Fig. 2(A and B).

The mean DSS for the low-risk stage II group was 98.9 months (95% CI: 90.9–106.9). The differences of DSS between the group that underwent chemotherapy versus the group not thus treated was not statistically significant (Log-Rank = 0634, $p = 0.426$).

The mean five-year DSS for the low-risk group was 96% (95% CI: 88.4–100%); 93.8% (95% CI: 81.8–100%) for the group that underwent chemotherapy versus 100% for the group not thus treated. The survival curves are shown in Fig. 3(A and B).

High-risk group

The high-risk group consisted of 145 subjects, 62.1% ($n = 90$) males and 37.9% ($n = 55$) females. The mean age at diagnosis was 70.9 years.

As for the administration of adjuvant chemotherapy, this was carried out in 49% ($n = 71$) of patients, while 35.9% ($n = 52$) did not undergo this procedure.

During the follow-up, 17.2% ($n = 25$) of patients had disease recurrence and 12.4% ($n = 18$) died from the disease.

The prognosis for high-risk patients who underwent adjuvant chemotherapy was compared to that for those who were not thus treated. The mean DFS for the high-risk stage II group was 96.5 months (95% CI: 89.9–103). In the group that underwent chemotherapy, the mean DFS was 98.8 months (95% CI: 90.3–107.2) versus 85 months (95% CI: 72.1–97.9) in the group not thus treated. The differences in DFS between the two groups are not statistically significant (Log-Rank = 2.598; $p = 0.107$).

The five-year DFS for high-risk stage II group was 80.5% (95% CI: 73.4–87.6%), with 83.4% (95% CI: 74.4–92.4%) for those patients who underwent chemotherapy and 68.8% (95% CI: 54.1–83.5%) for those not thus treated. The survival curves are shown in Fig. 4(A and B).

The mean DSS for high-risk stage II group was 102.8 months (95% CI: 97.5–108). Patients who underwent chemotherapy presented a mean DSS of 105.5 months (95% CI: 99.3–111.8) and those whose procedure was not carried out the mean DSS was 90.3 months (95% CI: 78.4–102.2). The differences in DSS between the two groups are statistically significant (Log-Rank = 4.337; $p = 0.037$).

The mean five-year DSS in high-risk stage II patients was 87.9% (95% CI: 81.8–94%); in patients undergoing chemotherapy this value was 88.9% (95% CI: 81.1–96.7%); and in patients not submitted to chemotherapy this value was 82.5% (95% CI: 70.3–94.7%).

The survival curves are shown in Fig. 5(A and B).

Discussion

One of the goals of our study was to determine DSS of patients with colon cancer, according to the 6th edition of the AJCC. The five-year DSS of our patients was as follows: stage I – 100%, IIA – 93%, IIB – 27.4%, IIIA – 75%, IIIB – 72.5%, IIIC – 51.1%; and IV – 28.3%. We found that the five-year DSS in our sample decreases with the progression of the stage, except for stage IIB that has the lowest survival of all, but with no statistically significant difference versus stages IIIC and IV. This later finding contradicts the literature,[7] although

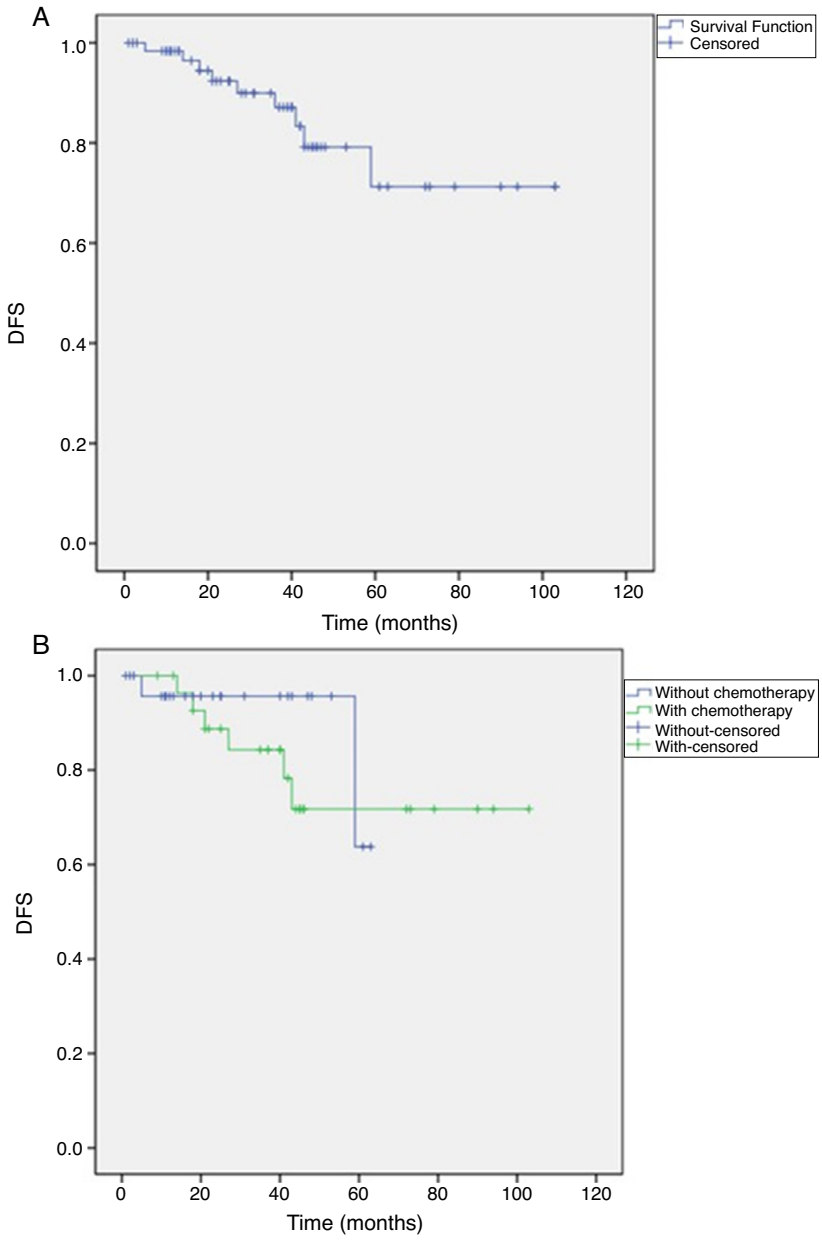

Fig. 2 – (A) DFS of low-risk stage II patients; (B) DFS according to the administration of chemotherapy, for low-risk stage II patients.

similar values are also observed.[17] The insufficient number of individuals in our sample for each stage may have been one factor responsible for the differences between our results and the literature findings, and also by the absence of statistically significant differences in DSS between some stages.

In our study, as in other studies reviewed, DSS for IIIA is higher than to DSS for IIB ($p = 0.001$).[17] Although care should be taken in interpreting this data (in the face of the low number of patients with stage IIB), this fact may be due to the consensual use of adjuvant chemotherapy in patients in stage III, and, on the other hand, to the controversial use of this procedure in patients with stage II.[16,17]

Reviewing the literature, we note that the use of adjuvant chemotherapy in patients in stage II is not consensual,[16] as several studies documenting the lack of benefit were published,[18–21] while other studies show evidence of gain with this procedure,[21–24] stressing that only small absolute benefits will be obtained in the face of the risk of overtreatment, including toxicity.[23] Thus, the use of adjuvant chemotherapy in patients with stage II will be only recommended for high-risk patients.[26,27]

For high-risk stage II patients, the means of DFS and DSS were higher in the group that underwent adjuvant chemotherapy (98.8 and 105.5 months, respectively) versus the group not treated (85 and 90.3 months, respectively), and five-year

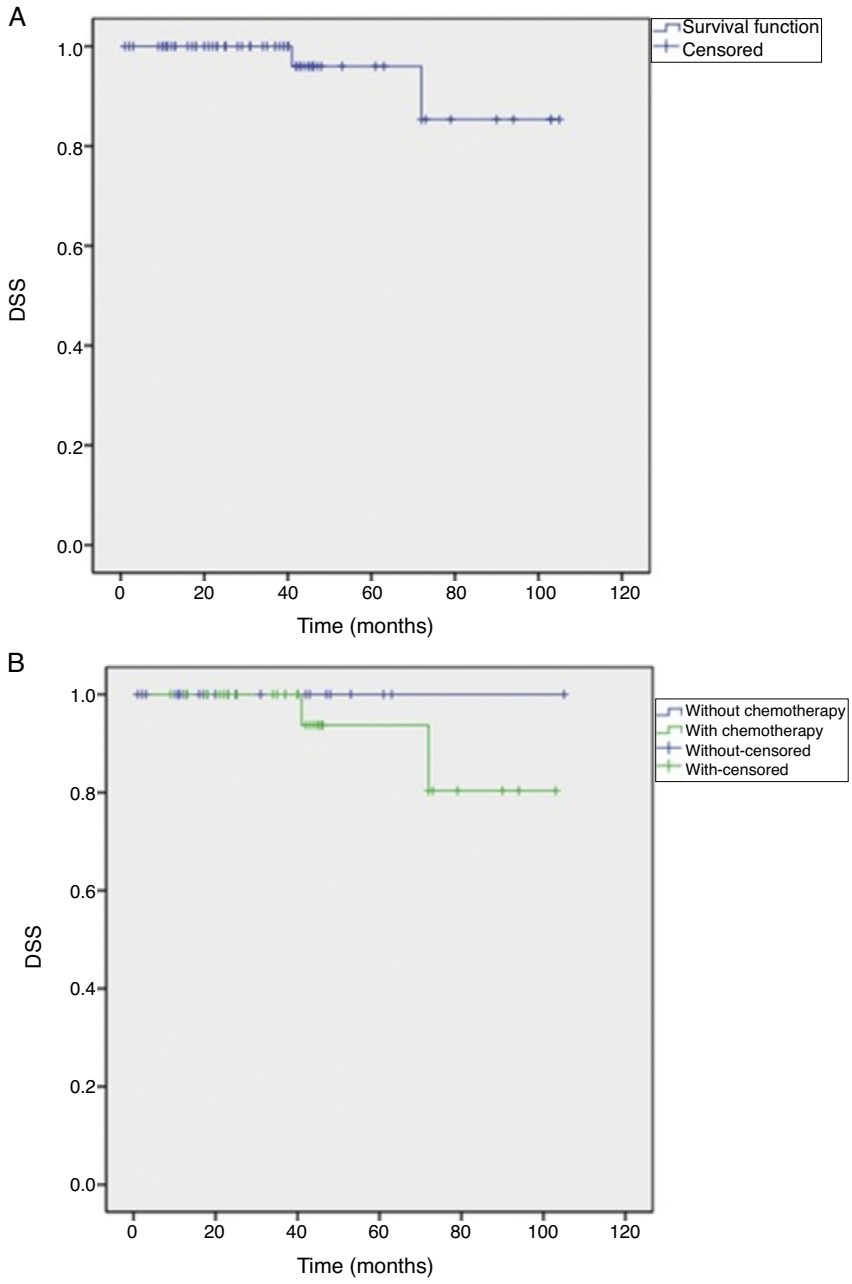

Fig. 3 – (A) DSS of low-risk stage II patients; (B) DSS according to the administration of chemotherapy, for low-risk stage II patients.

DFS and DSS were also higher in the group that underwent adjuvant chemotherapy (83.4% and 88.9%, respectively) compared with the non-treated group (68.8% and 82.5%, respectively). DFS values yielded not statistically significant results ($p = 0.107$); on the other hand, the results obtained for DSS were statistically significant ($p = 0.037$). These data are consistent with several studies showing the benefit of the adjuvant chemotherapy in terms of overall survival and DFS. Grande et al.[28] studied high-risk stage IIA patients, having found higher overall survivals and five-year DFS in patients receiving adjuvant chemotherapy, compared to patients submitted only to surgery. In the MOSAIC study, their authors demonstrated that the use of FOLFOX4 reduced the relative risk of relapse in 28% of high-risk stage II patients.[29] NSABP[21] showed some benefit with the use of chemotherapy in terms of survival for stage II patients with a poor prognosis (T4 tumors, obstruction, perforation). In the study by Kumar et al.,[30] these authors found statistically significant benefits of the adjuvant chemotherapy in terms of DFS and DSS only for patients with T4 tumors.

For low-risk stage II patients, the mean DFS is higher in the group that underwent chemotherapy (82.4 months) compared to the group not thus treated (59.2 months). This also occurred with the mean five-year DFS (71.8% vs 63.8%), but

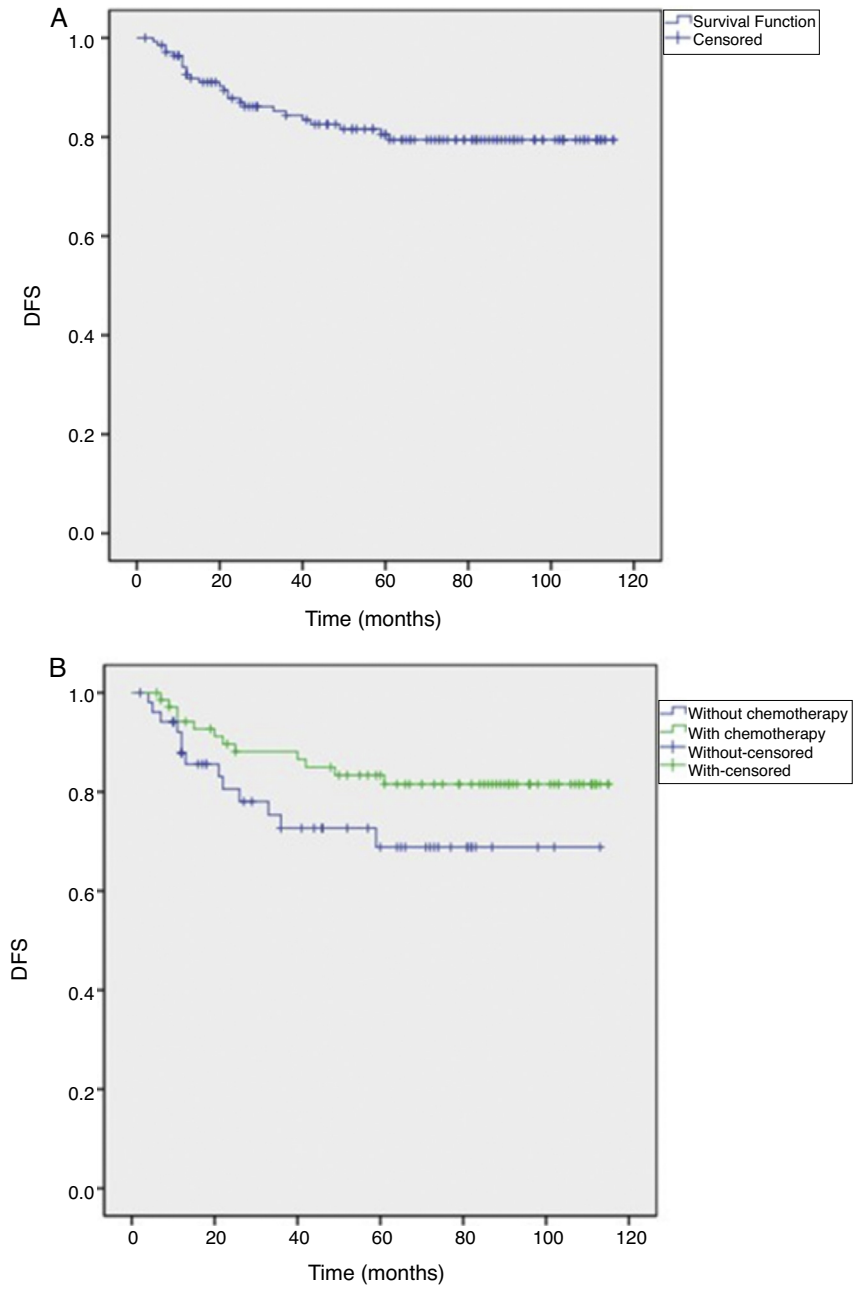

Fig. 4 – (A) DFS of high-risk stage II patients; (B) DFS according to the administration of chemotherapy, for high-risk stage II patients.

the differences between groups were not statistically significant ($p = 0.494$). The five-year DSS was 100% for the group that did not receive chemotherapy, and 93.8% for the group thus treated; but caution is needed in interpreting these data, taking into account the small number of events (two) in this patient group. The differences between groups were not statistically significant ($p = 0.426$). Grande et al.[28] found statistically significant differences in favor of the use of chemotherapy in terms of overall survival and of five-year DFS, however Kumar et al.[30] found that the use of chemotherapy was associated with worse DFS and DSS.

In our study the use of adjuvant chemotherapy, with respect to DSS, was only effective in high-risk stage II patients. Our study has its limitations: the small sample size compared to other studies, the high percentage of censored individuals and the lack of randomized groups. To study low- and high-risk stage II patients, we used samples of 55 and 123 patients, respectively. Patients were divided according to whether adjuvant chemotherapy was administered or not, and it was not taken into account the strength of the dose administered to each patient and the heterogeneity within each group, such as comorbidities.

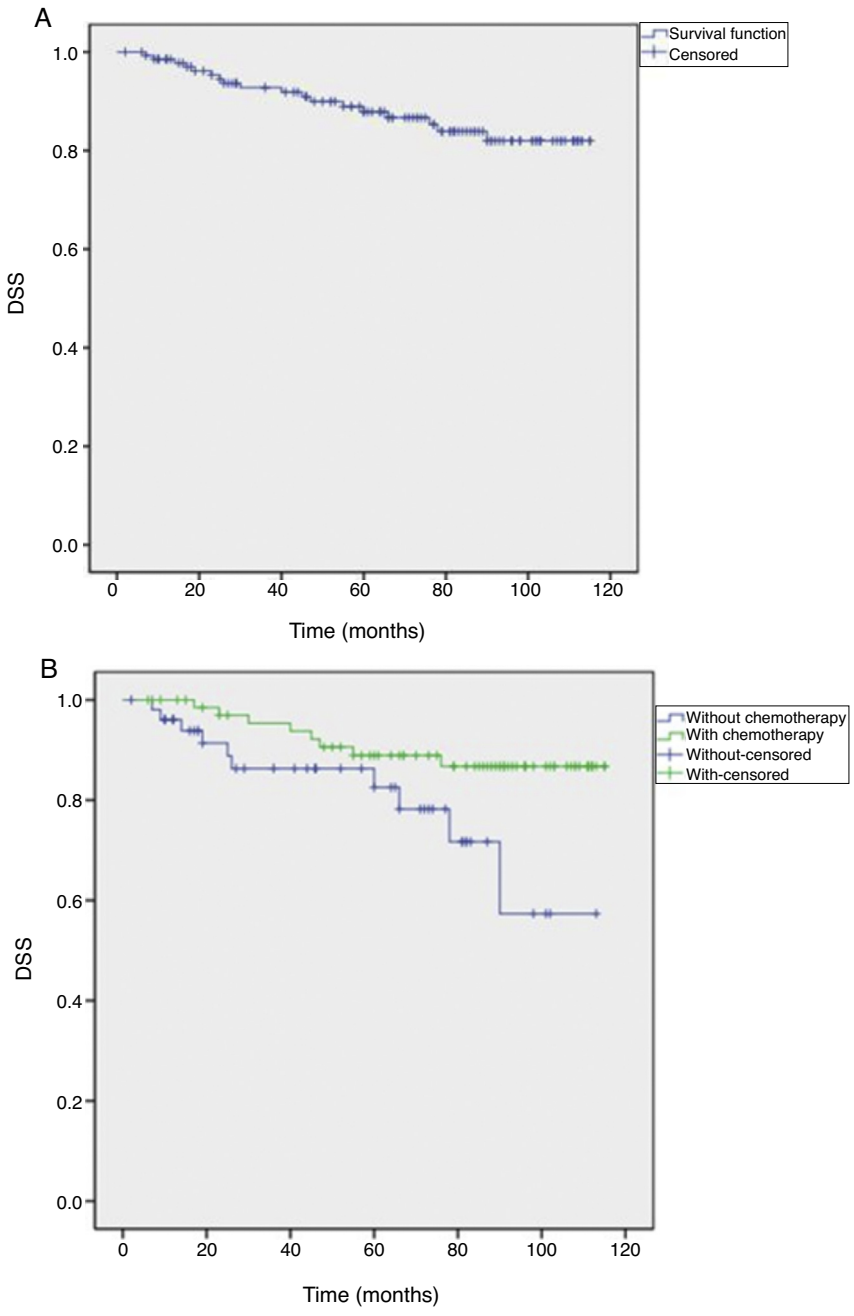

Fig. 5 – (A) DSS of high-risk stage II patients; (B) DSS according to the administration of chemotherapy, for high-risk stage II patients.

Conclusion

Pathologic staging is currently the main indicator of colon cancer prognosis, although individually this procedure cannot fully predict clinical outcome. According to the literature, we found in our sample that stage IIIA patients present higher DSS versus stage IIB patients ($p = 0.001$), although one must bear in mind the small number of patients in these two stages, and this can also justify why the absolute values of five-year DSS differ from those described in the literature. One can justify this situation with the consensual use of adjuvant chemotherapy in stage III patients, and its controversial use in stage II patients. For the remaining stages, the values are close to those described in the literature.

In our study, the use of adjuvant chemotherapy was effective for DSS only in high-risk stage II patients. For the remaining parameters evaluated, the results were controversial and not statistically significant, which could be related to the small number of patients, to censorship and to the absence of randomized study groups.

The controversy surrounding adjuvant chemotherapy administration to high- and low-risk stage II patients suggests the possibility of new markers, including molecular ones, to be

used to stratify the stage II risk and to define who will benefit from adjuvant therapy.

Conflicts of interest

The authors declare no conflicts of interest.

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