Introduction

Metastatic breast cancer (MBC) represents 20–30% of all breast cancers, and anthracyclines have proven to be a critical treatment choice. [1–4] However, pre-treatment with anthracyclines in an adjuvant setting precludes their repeated use because of cumulative cardiac toxicity [5,6]. Thus, from a treatment perspective, MBC patients can be arbitrarily regarded as anthracycline-pre-treated groups according to their regimens in the first two lines of chemotherapy. The overall survival (OS, 33.3 vs. 34.2 months, \( p = 0.179 \)), time to treatment failure of the first two lines of chemotherapy drugs (13.3 vs. 12.7 months, \( p = 0.104 \)) and best composite response rate (59.5% vs. 61.1%, \( p = 0.81 \)) were not significantly different between the two groups. Multivariate analysis showed that early anthracycline treatment was not a significant prognostic factor of OS (\( p = 0.052 \)). Thus, the results of this study show that anthracyclines may not be necessary as an early treatment option for AN-MBC.

For anthracycline-naive metastatic breast cancer (AN-MBC), early anthracycline treatment is a common practice. However, with the availability of newer chemotherapies, comparative studies on the efficacy of anthracyclines and non-anthracyclines as early treatments for AN-MBC are lacking. We collected retrospective clinicopathological data from 253 AN-MBC patients treated at National Taiwan University Hospital between 2001 and 2006. Patients were categorised into anthracycline or non-anthracycline groups according to their regimens in the first two lines of chemotherapy. The overall survival (OS, 33.3 vs. 34.2 months, \( p = 0.179 \)), time to treatment failure of the first two lines of chemotherapy drugs (13.3 vs. 12.7 months, \( p = 0.104 \)) and best composite response rate (59.5% vs. 61.1%, \( p = 0.81 \)) were not significantly different between the two groups. Multivariate analysis showed that early anthracycline treatment was not a significant prognostic factor of OS (\( p = 0.052 \)). Thus, the results of this study show that anthracyclines may not be necessary as an early treatment option for AN-MBC.

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Keywords:
Anthracyclines
Her2
Metastatic breast cancer
Overall survival
Palliative chemotherapy

The Breast 22 (2013) 1148–1154

Contents lists available at ScienceDirect
The Breast
journal homepage: www.elsevier.com/brst

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those who have been exposed to anthracyclines. This raises the question of whether modern non-anthracycline drugs are a better choice as one of the first two lines of chemotherapy for MBC. To our knowledge, there are currently no comparative studies that compare the efficacy of anthracycline and non-anthracycline regimens as the first two lines of palliative chemotherapy in AN-MBC patients.

This study investigates the question of whether anthracyclines should still be considered as one of the first two lines of palliative chemotherapy for AN-MBC patients in the modern era.

Materials and methods

This study was approved by the Research Ethics Committees of National Taiwan University Hospital. Between 1 January 2001 and 31 December 2006, we collected the clinical data of all female patients older than 18 years diagnosed with MBC. Patients with breast phyllodes tumour, sarcoma or lymphoma were excluded. These selection criteria produced a sample of 811 MBC patients. Of these patients, 409 patients who received anthracyclines as part of adjuvant or neo-adjuvant treatment were excluded for analysis. Additionally, to truly reflect the efficacy of chemotherapy agents, only those patients who had received at least two lines of chemotherapy drugs were included in our analyses. Patients who received only one line of chemotherapy drug over the course of treatment were excluded based on the assumption that the survival data of these patients might reflect poor patient compliance or the biological behaviour of the tumour rather than the efficacy of the chemotherapy drug. Among patients who did not receive anthracyclines as adjuvant or neo-adjuvant treatment, 149 received less than two lines of salvage chemotherapy and were excluded from this study. Overall, 253 patients met the selection criteria and were included for further analysis.

We collected demographic and clinicopathological data from patient’s medical charts. The variables included age, oestrogen receptor (ER) status, human epidermal growth factor receptor type 2 (Her2) status, extent of metastasis (visceral vs. non-visceral), the number of visceral metastases, history of adjuvant or neo-adjuvant chemotherapy, radiotherapy to the breast and the presence of metastatic disease (recurrent vs. de novo metastatic disease). We defined ER positivity as ≥5% of cancer cells staining positive on immunohistochemical (IHC) analysis. We defined Her2 positivity as a score of 3+ in Her2 IHC or the amplification of the Her2 gene as detected by fluorescence in situ hybridisation.

Each patient was assigned a group label according to the first and second line of the chemotherapy drugs she received. Those who received doxorubicin, epirubicin or liposomal doxorubicin as part of their first or second line of chemotherapy drugs were included in the anthracycline group. Patients who did not receive anthracyclines in the first two lines of chemotherapy were included in the non-anthracycline group.

Statistical analysis

We used SPSS version 17.0 (SPSS, Chicago, IL, USA) to conduct all statistical analyses. We followed up patients until death or as late as 31 August 2011. All patients lost to follow-up at our hospital were linked to the Death Registry Database of the Department of Health to check their survival status and date of death. We analysed the differences between clinicopathological features by using a chi-squared test for categorical data and Student’s t-test for continuous variables. The overall survival (OS) extended from the date of the start of the first chemotherapy drug administered for MBC to the date of death or censoring at the date of last follow-up. The time to treatment failure of the first two lines of chemotherapy drugs (TTF2) was defined from the date of the first cytotoxic chemotherapy agent to the end of the second line of cytotoxic chemotherapy treatment course. This period included the date of documented disease progression or the start of the third line of chemotherapy regimen or death, whichever occurred first. In only patients whose disease is under control — either responsive or stable — after chemotherapy will the sandwiched treatment be hormonal treatment. Patients who received maintenance therapy with hormonal agents or low-dose metronomic chemotherapy after the second line of cytotoxic chemotherapy were censored at the time of treatment initiation. We used the Kaplan–Meier method to estimate the median OS and TTF2 and used log-rank tests to compare survival differences. We used the Cox proportional hazards model to calculate the adjusted hazard ratio (HR) of the variables of OS and TTF2. The tumour response after chemotherapy treatment was recorded by a treating physician based on physical examination and radiological images. The best composite response rate (BCRR) was defined as the percentage of patients with at least a clinical response (partial response and complete response) at some time during their first or second lines of chemotherapy treatment [21]. All statistical tests were two-sided, and \( p < 0.05 \) was considered statistically significant.

Results

Basic characteristics of the study cohort

The median age at the time of the diagnosis of metastatic disease in the 253 patients in this sample was 53.5 years (range 28.8–84.9 years). Sixty percent and 48% of the patients were ER positive and Her2 positive, respectively. Only 2.4% of the Her2-positive patients did not receive trastuzumab or lapatinib during the entire course of treatment for MBC. The median follow-up time was 30.4 months (range 1.7–127.7 months). The average lines of chemotherapy received were 4.2. We recorded 160 and 180 events for the OS and TTF2 during the follow-up period, respectively. The median OS for the study cohort was 33.9 months (95% confidence interval (CI) 29.0–38.7). The 1-year and 5-year survival rates were 84.6% and 11.1%, respectively. The median TTF2 of the study cohort was 12.7 months (95% CI 10.9–14.5). The BCRR of the cohort was 60.5% (95% CI 54.2–66.7).

An anthracycline-containing regimen was one of the first two lines of cytotoxic chemotherapy in 109 (43.1%) patients. As many as 144 (56.8%) patients did not receive anthracyclines in the first two lines of cytotoxic chemotherapy. In the non-anthracycline group, 97 patients (97/144, 67.4%) never received any anthracycline during the entire course of treatment for MBC. Table 1 shows the demographic and clinicopathological characteristics of the anthracycline, non-anthracycline and the overall groups. The distributions of variables, including numbers of visceral metastases, were not significantly different between the two treatment groups.

As for the hormonal treatments, 71% (78/109) and 79% (113/144) of patients had hormonal treatment after the diagnosis of stage IV disease in the anthracycline and non-anthracycline groups, respectively, without significant difference (\( p = 0.129 \)). The mean lines of hormonal treatment between the two lines of chemotherapy were 0.45 and 0.43 for the anthracycline and non-anthracycline groups, respectively, without significant difference (\( p = 0.908 \)). In the subgroup of patients who had recurrent stage IV disease, 47% (24/51) and 52% (42/81) received adjuvant hormonal treatment in the anthracycline and non-anthracycline groups, respectively, without significant difference (\( p = 0.586 \)).

Components of the first two lines of chemotherapy

Table 2 shows the components of the first two lines of chemotherapy regimens. In the anthracycline group, the three most commonly used drugs in both the first and second lines of treatment
Table 1
Demographics and clinicopathological characteristics of the study population.

<table>
<thead>
<tr>
<th>Component</th>
<th>Whole cohort (N = 253)</th>
<th>Anthracycline group (N = 109)</th>
<th>Non-anthracycline group (N = 144)</th>
<th>p-Value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number (%)</td>
<td>Patients (%)</td>
<td>Patients (%)</td>
<td>Patients (%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.898</td>
</tr>
<tr>
<td>&gt;50 years old</td>
<td>149 (58.9)</td>
<td>65 (59.6)</td>
<td>84 (58.3)</td>
<td></td>
</tr>
<tr>
<td>≤50 years old</td>
<td>104 (41.1)</td>
<td>44 (40.4)</td>
<td>60 (41.7)</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
<td></td>
<td>0.299</td>
</tr>
<tr>
<td>Positive</td>
<td>155 (61.5)</td>
<td>63 (57.8)</td>
<td>92 (64.3)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>97 (38.5)</td>
<td>46 (42.2)</td>
<td>51 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Her2</td>
<td></td>
<td></td>
<td></td>
<td>0.526</td>
</tr>
<tr>
<td>Positive</td>
<td>120 (47.4)</td>
<td>49 (44.5)</td>
<td>73 (50.7)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>133 (52.6)</td>
<td>60 (55.1)</td>
<td>71 (49.3)</td>
<td></td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td></td>
<td></td>
<td></td>
<td>0.730</td>
</tr>
<tr>
<td>Present</td>
<td>213 (84.2)</td>
<td>93 (85.3)</td>
<td>120 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>40 (15.8)</td>
<td>16 (14.7)</td>
<td>24 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Pattern of metastatic disease</td>
<td></td>
<td></td>
<td></td>
<td>0.162</td>
</tr>
<tr>
<td>Recurrent</td>
<td>132 (52.2)</td>
<td>51 (46.8)</td>
<td>81 (56.3)</td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>121 (47.7)</td>
<td>58 (53.2)</td>
<td>63 (43.8)</td>
<td></td>
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<tr>
<td>Adjuvant or neoadjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td>0.782</td>
</tr>
<tr>
<td>Received</td>
<td>75 (29.6)</td>
<td>31 (28.4)</td>
<td>44 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Did not receive</td>
<td>178 (70.4)</td>
<td>78 (71.6)</td>
<td>100 (69.4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy to the breast</td>
<td></td>
<td></td>
<td></td>
<td>0.097</td>
</tr>
<tr>
<td>Received</td>
<td>58 (77.1)</td>
<td>30 (27.5)</td>
<td>28 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Did not receive</td>
<td>155 (22.9)</td>
<td>79 (72.5)</td>
<td>116 (80.6)</td>
<td></td>
</tr>
<tr>
<td>Mean number of visceral metastases</td>
<td>1.51</td>
<td>1.47</td>
<td>1.54</td>
<td>0.586</td>
</tr>
<tr>
<td>Mean lines of chemotherapy received</td>
<td>4.2</td>
<td>4.0</td>
<td>4.4</td>
<td>0.625</td>
</tr>
</tbody>
</table>

\(^a\) p-values were analyzed by two sided chi-square test, except for mean lines of chemotherapy received, which was analyzed by Student’s t test.

\(^b\) Estrogen receptor status is uncertain for one patient.

were anthracyclines, cyclophosphamide and 5-fluorouracil (5-FU).
The three most commonly used drugs in the non-anthracycline group were 5-FU, vinorelbine and paclitaxel for both the first and second lines of treatment. Chemotherapy drugs were predominantly used in a combinational fashion in both the anthracycline group (first and second lines, 93.5% and 75.2%) and the non-anthracycline group (first and second lines, 81.9% and 68.1%).

OS, TTF2 and BCRR in different treatment groups

As Fig. 1A shows, the median OS was not significantly different between the two treatment groups (p = 0.179). The median OS values for the anthracyline and non-anthracyline groups were 33.3 (95% CI 25.2–41.4) and 34.2 (95% CI 28.8–39.7) months, respectively. As Fig. 1B shows, TTF2 was also not significantly different between the two treatment groups (p = 0.104). The median TTF2 values for the anthracyline and non-anthracyline groups were 13.3 (95% CI 5.9–20.8) and 12.7 (95% CI 10.8–14.5) months, respectively. The BCRR values of the anthracyline and non-anthracyline groups were 59.5% and 61.1%, respectively, and were not significantly different (p = 0.81).

Fourteen patients had a clinical complete response after the first two lines of salvage chemotherapy treatment. Within this group, eight patients were treated with anthracycline-containing regimens and six were treated with non-anthracycline-containing regimens.

De novo MBC patients (i.e., patients whose first breast cancer diagnosis was a stage IV disease) were selected for further analysis to minimise the influence of previous adjuvant treatment on the survival of metastatic disease. The survival curves of OS and TTF2...
for both treatment groups essentially overlapped, as shown in Fig. 2. Early anthracycline treatment was not superior to non-anthracycline treatment in terms of OS and TTF2, for patients with de novo MBC. The BCRR values were also similar for both treatment groups (67.2 vs. 66.7%; odds ratio 1.03, 95% CI 0.48–2.19, \(p = 0.94\)).

### Analyses according to molecular sub-types

We also analysed the differential effects of anthracycline and non-anthracycline treatment in various breast cancer sub-types, categorised as ER+/Her2−, ER+/Her2+, ER−/Her2+ and ER−/Her2−. Figs. 3 and 4 show the Kaplan–Meier curves of the OS and TTF2, respectively. The early use of an anthracycline-containing regimen as the first or second line of chemotherapy did not yield a statistically significantly better OS or TTF2 than non-anthracycline-containing regimens among the various sub-types. However, in the ER+/Her2+ sub-type, early anthracycline treatment showed a trend for better OS (median OS 58.0 vs. 31.2 months, \(p = 0.081\)). By contrast, in the ER+/\(\neg\)/Her2+ sub-type, the OS values were comparable in both treatment groups (median OS 24.3 vs. 43.4 months, \(p = 0.352\)). The difference in TTF2 values between the anthracycline and non-anthracycline groups was non-significant for all subgroups (Fig. 4).

### Multivariate analysis of prognostic factors of OS

Table 3 shows the results of the multivariate Cox proportional hazard model of the OS of the study population. In the multivariate model, the ER and Her2 status and the presence of visceral metastasis were all significant prognostic factors for OS. This model shows a trend towards early anthracycline treatment (anthracycline group) as a significant prognostic factor (HR 0.72, 95% CI 0.52–1.00, \(p = 0.052\)). However, if the ER−/Her2+ sub-type patients were excluded from the multivariate analysis model, the trend towards a better prognosis disappeared for early anthracycline treatment (HR 0.82, 95% CI 0.56–1.18, \(p = 0.28\)). The prognostic factors for TTF2 were ER (HR 0.74, 95% CI 0.54–0.99, \(p = 0.046\)) and the presence of visceral metastasis (HR 1.54 95% CI 1.00–2.36, \(p = 0.049\)). Early anthracycline treatment showed a trend towards longer TTF2 (HR 0.74, 95% CI 0.55–1.00, \(p = 0.054\)) but, similarly to the OS model, this trend disappeared when ER−/Her2+ patients were excluded (HR 0.77 95% CI 0.54–1.09, \(p = 0.14\)).

### Discussion

The standard salvage treatment for AN-MBC in the modern era has not been established. This study shows that the efficacy of modern non-anthracycline-containing regimens as the first two lines of chemotherapy in AN-MBC is comparable with anthracycline-containing regimens in terms of OS, TTF2, BCRR and clinical complete response rates. To our knowledge, this is the first study to demonstrate that delaying the use of anthracyclines to third or later lines of salvage chemotherapy for AN-MBC patients does not negate the odds of survival. As adjuvant studies regarding non-anthracycline-based chemotherapy mature [10–15], an increasing number of MBC patients are likely to be anthracycline-naive before the start of palliative chemotherapy. The results of this study, although retrospective in nature, can help support clinical decisions regarding the selection of early lines of palliative chemotherapy regimens.

The majority of patients, in both the anthracycline and non-anthracycline group, were treated with combination chemotherapy. It was traditionally considered that combination chemotherapy could achieve a higher clinical complete response rate, which may translate into a chance of long-term survival [19,22,23]. However, this concept was developed in an era when the treatment of MBC was dominated by anthracycline-based treatment [19]. In this study, six out of the eight patients who had a clinical complete response in the anthracycline group survived longer than 5 years, whereas only one out of six patients who achieved clinical complete response remained alive 5 years after treatment started in the non-anthracycline group. This result implies that achieving a clinical complete response may not be a critical factor for long-term survival in patients treated with non-anthracycline-containing regimens. Further study is needed to elaborate the mechanisms underlying these results.

In molecular sub-type analyses, there is a non-statistically significant trend showing that patients with early anthracycline treatment had more clinical benefits in the ER−/Her2+ sub-type in terms of OS. By contrast, the other molecular subgroups exhibited no survival benefit. Her2 positivity has been considered as a predictive marker for responsiveness to anthracycline. [24] However, the role of ER positivity in addition to Her2 status for the prediction of anthracycline treatment benefit remains uncertain. ER−/Her2+ early-stage breast-cancer patients have a higher pathological response rate after anthracycline-based neo-adjuvant treatment [25], and the interaction between anthracycline treatment and Her2 amplification was only statistically significant in ER-negative early-stage breast-cancer patients [26,27]. Conversely, although ER+/Her2+ breast cancer is less responsive to anthracycline treatment [25], the ER+/Her2− sub-type is correlated with topo-isomerase II alpha (TOP2A) amplification [28], which is another possible predictive factor for anthracycline responsiveness [29,30]. However, the results of the subgroup analyses must be interpreted...
cautiously. Future analysis regarding the efficacy of anthracyclines in Her2+ breast cancer should incorporate hormone status as one of the variables to delineate the true effect.

Certain limitations of our study should be addressed. First, this study is a retrospective study from a single centre with relatively small number of patients. Therefore, the results must be interpreted with caution. Second, disease severity may interfere with chemotherapy drug selection in treating MBC. However, a balanced demographic and clinicopathological distribution in both treatment groups, as shown in Table 1, represents a minimal selection bias. Previous Phase II studies conducted in our hospital have demonstrated acceptable efficacy of non-anthracycline-containing regimens as first-line salvage chemotherapy for MBC [31,32]. Therefore, it is not uncommon for doctors to prescribe non-anthracyclines as an early salvage option even for cases with a more severe condition. Finally, the percentage of Her2-positive

**Fig. 3.** The Kaplan–Meier survival curves for overall survival (OS) of molecular subtype analyses according to different treatment groups (a) Estrogen receptor (ER) +/Human epidermal growth factor 2 (Her2)+ subtype (b) ER+/Her2+ subtype (c) ER−/Her2+ subtype (d) ER−/Her2− subtype.

**Fig. 4.** The Kaplan–Meier survival curves for time to treatment failure of the first 2 lines of chemotherapy drugs (TTF2) of molecular subtype analyses according to different treatment groups (a) Estrogen receptor (ER) +/Human epidermal growth factor 2 (Her2)+ subtype (b) ER+/Her2+ subtype (c) ER−/Her2+ subtype (d) ER−/Her2− subtype.
disease was higher than the average population. The quality of Her2 status judgement in our hospital should not be a critical issue because another study by Lin et al. conducted in the same hospital showed 20% of patients with Her2-positive disease in early-stage breast cancer [33], reflecting the reliability of Her2 positivity in our hospital. Conversely, the higher percentage of Her2-positive disease may be a reflection of the higher recurrence rate of patients with Her2-positive disease [34,35]. In our unpublished data regarding an MBC cohort in which anthracyclines were used as part of the adjuvant chemotherapy, the percentage of Her2-positive disease was also approximately 45.

Sequential single-agent chemotherapy is currently the preferred method of treating MBC [36,37]. Although anthracyclines and taxanes are still suggested as first-line choices for treating AN-MBC when applying sequential single-agent chemotherapy treatment strategy in the recommendation from 1st International consensus guidelines for advanced breast cancer (ABC1) [36], other single-agent chemotherapies such as capetitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient, are also listed as options for first-line chemotherapy choices [36]. The data in this study were obtained from combined chemotherapy regimens for the first two lines of chemotherapy treatment. Therefore, it is uncertain whether this result — OS was similar between the anthracycline and non-anthracycline groups — could be extrapolated to patients treated with sequential single-agent chemotherapy. The MBC community would greatly benefit from additional research to identify the optimal sequence when using anthracyclines in sequential mono-chemotherapy treatment paradigms.

In summary, we have presented a retrospective study of AN-MBC patients showing that the efficacy of anthracyclines and modern non-anthracycline chemotherapy drugs was not significantly different in terms of OS, TTF2 and BCRR in patients other than ER−/Her2+ sub-type. The ER−/Her2+ sub-type patients may experience more clinical benefits from early anthracycline treatment if only one line of trastuzumab-containing regimen is prescribed. The results of this study show that future prospective clinical trials are warranted.

Conflict of interest

The authors declare no conflict of interests. No sponsor participated in this study. This study was approved by the Research Ethics Committees of National Taiwan University Hospital.

Table 3

<table>
<thead>
<tr>
<th>Factors</th>
<th>Hazard ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline versus non-anthracycline</td>
<td>0.72 (0.52–1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Age over 50</td>
<td></td>
<td></td>
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<tr>
<td>Yes versus no</td>
<td>0.92 (0.67–1.27)</td>
<td>0.620</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive versus negative</td>
<td>0.66 (0.47–0.96)</td>
<td>0.027</td>
</tr>
<tr>
<td>Her2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive versus negative</td>
<td>0.68 (0.48–0.97)</td>
<td>0.034</td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present versus absent</td>
<td>2.56 (1.48–4.46)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Pattern of metastasis</strong></td>
<td></td>
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<tr>
<td>Recurrent versus de novo</td>
<td>1.07 (0.78–1.47)</td>
<td>0.674</td>
</tr>
<tr>
<td>Adjuvant/neoadjuvant chemotherapy</td>
<td>0.98 (0.63–1.53)</td>
<td>0.929</td>
</tr>
<tr>
<td>Yes versus no</td>
<td>0.93 (0.63–1.34)</td>
<td>0.694</td>
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**References**


