Randomized Trial of Vitamin C/E Complex for Prevention of Radiation-Induced Xerostomia in Patients with Head and Neck Cancer

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract
Objective. The present study was conducted to determine the preventive efficacy of vitamin C/E complex supplementation for radiotherapy (RT)-induced xerostomia in patients with head and neck cancer.

Study Design. Prospective, double-blinded, randomized, placebo-controlled study.

Setting. A single tertiary referral institution.

Subjects and Methods. The trial group (n = 25) received antioxidant supplements (100 IU of vitamin E + 500 mg of vitamin C) twice per day during RT, while the control group (n = 20) received an identical placebo. Pre-RT and 1 and 6 months post-RT, patient-reported xerostomia questionnaires, observer-rated xerostomia score, and salivary scintigraphy were serially obtained to compare xerostomia severity between the 2 groups.

Results. The trial group showed greater improvements in xerostomia questionnaire and score at 6 months post-RT when compared with those at 1 month post-RT (P = .007 and .008, respectively). In contrast, the control group showed no changes between 1 and 6 months post-RT. By salivary scintigraphy, there was no difference in maximal accumulation or ejection fraction between the 2 groups. However, the trial group maintained significantly better oral indices at the presalivary gland (P = .01) and poststimulatory (P = .009) stages at 1 month post-RT, compared with the control group. At the final follow-up, there was no difference in overall survival and disease-free survival between the 2 groups.

Conclusions. Our data suggest that short-term supplementation with an antioxidant vitamin E/C complex exerts a protective effect against RT-induced xerostomia.

Keywords
radiotherapy, vitamin, xerostomia, head-and-neck cancer, randomized trial

Xerostomia is one of the most common side effects related to radiotherapy (RT) for head and neck cancer (HNC). This uncomfortable condition negatively affects the quality of life, even in potentially cured cancer patients, because irradiation of the head and neck leads to changes in the volume, consistency, and pH of secreted saliva. As a result, oral discomfort, pain, and difficulty in speaking, chewing, and swallowing can occur during the acute or late period following RT. Xerostomia eventually leads to major health problems, as well as social regression with a high level of distress.

To overcome these issues, various strategies—such as salivary gland–sparing radiation techniques (eg, intensity-modulated RT and 3-dimensional RT), concomitant use of amifostine or pilocarpine, and surgical transfer of the submandibular gland during or after RT—have been tested to minimize RT-induced xerostomia, with varying degrees of efficacy. Yet, these attempts are still far from practical clinical application due to the difficulty of administration

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(eg, intravenous and subcutaneous) and the concerns regarding toxic side effects.\textsuperscript{5,13}

Since irradiation causes damage to both normal cells and cancer cells, primarily through free radical formation, antioxidants have been suggested to decrease irradiation toxicity to normal cells by neutralizing free radicals.\textsuperscript{7,19-23} However, the oncologic safety of antioxidant supplementation in cancer patients during chemortherapy or RT remains debated.\textsuperscript{23-26} Thus, we hypothesized that vitamin C or E, important ingredients of natural antioxidants, can act as a radioprotector of the salivary glands, if administered at an appropriate dosage and duration. Unfortunately, few publications have addressed the effect of antioxidants on post-RT xerostomia in patients with HNC.\textsuperscript{7,19} The objective of the current clinical trial was to investigate the clinical effect of vitamin C/E complex supplementation during RT for HNC in terms of preventing RT-induced xerostomia.

### Materials and Methods

#### Study Population and Design

This prospective, randomized, double-blinded, placebo-controlled study was conducted from July 1, 2008, to May 30, 2010. The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from patients before randomization. Eligible patients were (1) aged \textgreater 18 years, (2) diagnosed with biopsy-proven HNC, and (3) treated with \textgreater 4000 cGy intensity-modulated RT. Patients were excluded if they had (1) simultaneous malignancies, (2) Karnofsky performance score \textless 60\%, (3) previous adverse reactions to the investigational product or salivary scintigraphy, (4) history of vitamin medication within the past 3 months, or (5) salivary gland excision during surgery.

#### Randomization and Intervention

Patients who provided written informed consent were randomized into 2 intervention arms: vitamin C/E complex supplementation (trial group) or placebo supplementation (control group). The randomization sequence, which was concealed, was generated as a block permutation by a research coordinator (E.H.K.) using computer software. Serial numbers were allocated to consecutive patients throughout the study, to maintain the concealment of group allocation. The patients and study personnel were also blinded to the allocation.

Once enrolled, the trial group received the investigational products: an oral pill of 100 IU of vitamin E \(+500\) mg of vitamin C, taken twice per day, resulting in ingestion of 200 IU of vitamin E and 1000 mg of vitamin C daily. The placebo group received an identical placebo pill (ie, no investigational product) twice per day as in the trial group. Both groups started the supplements 1 week before RT and continued for 1 month after its completion (average duration, 3 months).

#### Assessment

The severity of xerostomia was evaluated before RT (baseline) and at 1 and 6 months after its completion. The following tools were used to assess xerostomia: (1) patient-reported xerostomia questionnaire (XQ), (2) observer-rated xerostomia score (XS), and (3) salivary scintigraphy.\textsuperscript{17-19} As described in previous reports, the 8-item XQ was reported by patients: (1) a parched feeling in the mouth, (2) stickiness in the mouth, (3) strong desire to drink, (4) pain in the oral cavity, (5) taste abnormality, (6) speech impairment, (7) difficulty in mastication, and (8) difficulty in swallowing. Also, the 9-item XS was rated by 2 independent physicians (M.K.C., Y.I.S.): (1) dryness of the oral mucosa, (2) redness of the oral mucosa, (3) oral ulcer, (4) coating, (5) smoothing, (6) wrinkles and creases on the tongue surface, (7) cracks on the tongue surface, (8) redness, and (9) dryness of the mucosa of the oropharynx. Each item was scored or rated semiquantitatively on a 4-point scale, from 0 (no complaints or normal) to 3 (severe discomfort or worse findings); thus, higher XQ and XS scores indicated worse discomfort or findings.

Salivary scintigraphy was performed as described previously.\textsuperscript{19} Briefly, after confirmation that patients were well hydrated, a bolus of 259 MBq (7 mCi) \textsuperscript{99m}Tc-sodium pertechnetate was injected intravenously. A mobile scintillation camera (Triad XLT; Triionox Research Laboratory, Twinsburg, Ohio) with a small field of view was used to obtain images up to 40 minutes after injection (128 \times 128–pixel matrix at 60 seconds per frame). To measure excretory function, oral stimuli (2 mL of lemon juice) were administered intraorally, while patients were asked to refrain from any mechanical stimulation (swallowing or chewing) of salivary flow during the imaging. Regions of interest were marked over the parotid and submandibular glands, and corresponding time-activity curves were drawn to calculate the functional parameters: maximal accumulation (%), ejection fraction (%), and the prestimulatory and poststimulatory oral index (%). Maximum accumulation was defined as the value of (peak activity before stimulation – initial activity at 1 minute after radiotracer injection) divided by peak activity before stimulation. The response of the salivary gland to lemon juice was noted on the time-activity curve as a sharp decline in the activity in the gland with a subsequent slow buildup. Then, the ejection fraction in each salivary gland was calculated as the amount of radioactivity cleared from the gland divided by the preclearance activity. The semiquantitative oral radioactivity index was also calculated from the time-activity curve.

#### Statistical Analysis

An intent-to-treat analysis was performed on all initially allocated patient groups. Continuous variables are reported as mean \(\pm\) SD. A 2-tailed Student’s \(t\) test and \(\chi^2\) analysis were used to evaluate the nonequality of measures between the 2 groups. The Mann-Whitney \(U\) test or Kruskal-Wallis test was applied to compare nonparametric data. Disease-free survival and overall survival were analyzed by Kaplan-Meier estimates, and a log-rank test was used to compare...
survival rates. Statistical significance was taken as a 2-sided $P$ value $< .05$ through PASW Statistics 22 (SPSS Inc, Chicago, Illinois).

**Results**

**Demographic Data**

Initially, a total of 139 patients with HNC were assessed for eligibility; 63 did not meet the criteria; and 24 refused to participate in the trial. Therefore, 52 volunteers were enrolled and randomly assigned to the trial group ($n = 26$) and placebo group ($n = 26$; Figure 1, CONSORT diagram). In the control group, 2 patients showed poor compliance with study medication and at 1 month post-RT refused to participate further. At 6 months post-RT, 2 more patients refused to participate (poor compliance), and 2 patients were dropped out due to disease recurrence. In the trial group, 1 patient refused to continue with the trial at 6 months post-RT. No significant adverse events or side effects related to study medication were noticed or reported throughout the trial. Finally, clinical data were analyzed for 25 patients in the trial group and 20 patients in the control group. The demographic data of 45 patients in the study are presented in Table 1. There was no significant difference in sex distribution and mean age between the 2 groups. The most common primary site was the larynx, followed by the pharynx and the oral cavity in both groups. According to the American Joint Committee on Cancer staging system, the number of patients of advanced clinical stage (III-IV) was higher than that of early stage (I-II) in both groups.

**Surgery and RT**

The mean radiation dosage was $60 \pm 13$ Gy for the trial group and $59 \pm 20$ Gy for the control group ($P = .20$). There was no difference in the mean radiation dosage to the salivary glands (control group vs trial group: parotid gland, $12 \text{ vs } 14$ Gy, $P = .82$; submandibular gland, $25 \text{ vs } 23$ Gy, $P = .27$). RT was conducted with or without concurrent chemotherapy (CCRT) with the intent of postsurgical adjuvant or definitive treatment, which was based on clinicopathologic information according to the treatment decision of the multidisciplinary tumor board meeting. In the control group, RT was performed in 6 patients (1 adjuvant, 5 definitive) and CCRT in 14 (8 adjuvant, 6 definitive). Similarly, adjuvant CCRT was the most common modality in the trial group, followed by definitive RT or CCRT, and there was no significant difference between the 2 groups ($P = .75$).

**Xerostomia Questionnaire and Scoring**

The assessment outcomes of salivary gland function are presented in Table 2 and Figure 2. According to the patient-reported XQ, all patients presented symptomatic discomfort due to xerostomia, most severely at 1 month post-RT, suggesting aggravation of xerostomia in the early period post-RT. Specifically, in the trial group, XQ at 1 month post-RT was higher (meaning worse symptoms) than at baseline.
The XS in the trial group was significantly higher at 1 month post-RT than at baseline ($P = .004$), and XS was significantly improved at 6 months when compared with 1 month post-RT ($P = .008$). In the control group, XS did not show any improvement at 6 months post-RT (XS at 1 vs 6 months, $P = .47$), despite a significant increase at 1 month post-RT compared with baseline ($P = .004$; Figure 2B).

**Table 1. Subject Demographics.**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 20)</th>
<th>Trial (n = 25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>18:2</td>
<td>22:3</td>
<td>.79</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>61.6 ± 9.6</td>
<td>56.6 ± 11.3</td>
<td>.79</td>
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<tr>
<td>Cancer sites</td>
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<td></td>
<td>.92</td>
</tr>
<tr>
<td>Larynx</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
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<td>4</td>
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</tr>
<tr>
<td>Pharynx</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>AJCC stage</td>
<td></td>
<td></td>
<td>.92</td>
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<tr>
<td>I-II</td>
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</tr>
<tr>
<td>III-IV</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy type</td>
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<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
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<tr>
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<td>4</td>
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<tr>
<td>Definitive</td>
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<td>5</td>
<td></td>
</tr>
<tr>
<td>CCRT</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Definitive</td>
<td>6</td>
<td>5</td>
<td></td>
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<tr>
<td>Radiation dose, Gy</td>
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<td></td>
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<tr>
<td>Whole field, mean ± SD</td>
<td>59 ± 20</td>
<td>60 ± 13</td>
<td>.20</td>
</tr>
<tr>
<td>Salivary glands, mean</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Parotid</td>
<td>12</td>
<td>14</td>
<td>.82</td>
</tr>
<tr>
<td>Submandibular</td>
<td>25</td>
<td>23</td>
<td>.27</td>
</tr>
</tbody>
</table>

**Abbreviations:** AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiation therapy.

aUnless indicated otherwise, values are presented as n, and P values are based on chi-square test.
bMann-Whitney test.

**Table 2. Subjective and Objective Measures of Salivary Gland Function in the Control and Trial Groups at Preradiotherapy and at 1 and 6 Months after Completion of Radiotherapy.**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 20)</th>
<th></th>
<th>Trial (n = 25)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-RT</td>
<td>1 mo</td>
<td>6 mo</td>
<td>Pre-RT</td>
</tr>
<tr>
<td>XQ</td>
<td>4.6 ± 3.8</td>
<td>7.0 ± 4.5</td>
<td>7.0 ± 4.6</td>
<td>5.4 ± 4.3</td>
</tr>
<tr>
<td>XS</td>
<td>1.7 ± 1.4</td>
<td>3.9 ± 2.4</td>
<td>3.3 ± 2.3</td>
<td>2.8 ± 2.3</td>
</tr>
<tr>
<td>Salivary scintigraphy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid</td>
<td>61.8 ± 11.5</td>
<td>56.6 ± 10.3</td>
<td>46.1 ± 25.2</td>
<td>59.6 ± 12.4</td>
</tr>
<tr>
<td>SMG</td>
<td>38.1 ± 13.3</td>
<td>33.3 ± 13.9</td>
<td>27.4 ± 16.7</td>
<td>39.6 ± 15.9</td>
</tr>
<tr>
<td>EF, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotid</td>
<td>30.5 ± 20.2</td>
<td>24.8 ± 20.5</td>
<td>24.2 ± 23.6</td>
<td>29.9 ± 17.0</td>
</tr>
<tr>
<td>SMG</td>
<td>24.4 ± 17.2</td>
<td>17.8 ± 18.9</td>
<td>17.1 ± 20.0</td>
<td>22.9 ± 12.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** EF, ejection fraction; MA, maximal accumulation; RT, radiotherapy; SMG, submandibular gland; XQ, patient-reported xerostomia questionnaire; XS, observer-rated xerostomia score.

*aValues presented as mean ± SD.*
Salivary Scintigraphy

Representative images of salivary scintigraphy during the poststimulatory phase pre- and post-RT are presented in Figure 3. One patient (Figure 3A) showed relatively well-preserved oral salivation as compared with baseline; in contrast, another patient (Figure 3B) showed markedly decreased salivary flow into the oral cavity, as compared with the baseline image. Maximal accumulation of $^{99m}$Tc-sodium pertechnetate into the parotid glands was not different between the 2 groups (at 1 month post-RT, $P = .86$; at 6 months post-RT, $P = .15$). Also, ejection fraction of the parotid glands did not differ between the 2 groups (at 1 month post-RT, $P = .57$; at 6 months post-RT, $P = .68$). Similar findings were observed in the submandibular glands (maximal accumulation: at 1 month post-RT, $P = .73$; at 6 months post-RT, $P = .96$; ejection fraction: at 1 month post-RT, $P = .40$; at 6 months post-RT, $P = .90$). Notably, the trial group maintained significantly better oral indices at the prestimulatory ($P = .01$) and poststimulatory ($P = .009$) stages at 1 month post-RT when compared with the control group (Figure 2C, D).

Oncologic Outcome

Oncologic safety of antioxidant medication during RT was investigated by comparing survival estimates between the 2 groups. The mean overall survival duration (Figure 4A) of the control group was 69.3 months, and that of the trial group was 65.9 months (log-rank test, $P = .75$). Similarly, the mean disease-free survival duration (Figure 4B) was 60.3 months for the control group and 59.6 months for the trial group (log-rank test, $P = .87$).

Discussion

This study demonstrated that short-term supplementation of vitamin C/E complex during RT might preserve the function of the major salivary glands, as evidenced by greater improvements between 1 and 6 months post-RT in the xerostomia survey (XQ, XS) and by better oral index at 1 month post-RT (salivary scintigraphy) as compared with the placebo-controlled group. This is the first prospective trial of antioxidants to focus on RT-induced xerostomia in HNC patients.

According to a recent randomized controlled trial, long-term (3 years) supplementation with antioxidant vitamins (alpha-tocopherol and beta-carotene) could reduce the acute adverse effect of RT on the mucosa of the larynx, pharynx, and esophagus. However, the authors raised concern regarding use of high doses of antioxidants, since this might compromise radiation treatment efficacy; therefore, they discontinued supplementation of beta-carotene during
The duration and dosage of antioxidant supplementation in our study were determined carefully because of these concerns about the use of antioxidants during cancer treatment, which stem from the uncertainty over their oncologic safety. Experimental data in cancer cells and animal models show that antioxidants preferentially protect normal cells over cancer cells from radiation-induced oxidative damage; therefore, the use of antioxidants may reduce RT-related adverse effects. However, high doses of antioxidants as adjuvant therapy might compromise radiation treatment efficacy by protecting cancer cells against radiation damage.

To ameliorate the risk of reducing the efficacy of cancer treatment, we used a commercially available, over-the-counter vitamin C/E complex regimen, which may be more feasible in clinical practice. Based on human studies, oral supplementation with vitamin C of 10 g/d and vitamin E of up to 10,000 IU is defined as a high dose and inhibits the growth of cancer cells without affecting that of normal cells. Given that the doses used in the present study were lower than “high doses,” the protocol would likely achieve the study aim without compromising the cancer treatment. To confirm this hypothesis, long-term oncologic outcomes were compared (mean follow-up, 53 months); no difference in overall survival and disease-free survival was observed.

The Radiation Therapy Oncology Group’s Acute Radiation Morbidity Scoring Criteria is a recognized instrument for the assessment of acute radiation adverse effect and is used widely in clinical trials. However, it is an observer-rated system and lacks specific items for xerostomia and related discomfort. The survey tools used in the current study (patient-reported XQ and observer-rated XS) were developed by Sugano et al for evaluation of xerostomia and pharyngoxerostomia. Although psychometric testing has not been performed, XQ and XS contain items specific to the evaluation of xerostomia. More important, we confirmed that XQ and XS were shown to be feasible and reliable for assessment of the response after xerostomia and globus management, with acceptable interobserver variability. In accordance with a previous report, both XQ and XS during the early period after RT were worse than at baseline. These data underscore the importance of early intervention to relieve xerostomia symptoms and findings during the acute period after RT. Furthermore, they support the

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Figure 3. Representative images from salivary scintigraphy show distinct contrasts in excreted $^{99m}$Tc-sodium pertechnetate into the oral activity at the poststimulatory phase (A, well preserved; B, severely decreased) as compared between pre- and postradiotherapy.

Figure 4. Oncologic outcomes (A, overall survival; B, disease-free survival) in the control and trial groups.
rational of our starting the intervention 1 week before RT and continuing it until 1 month afterward.

Salivary scintigraphy is a well-established imaging modality for semiquantitative assessment of the uptake and excretion function of the parotid and submandibular glands; thus, it is useful for post-RT surveillance of salivary function.\textsuperscript{32,33} Oral indices can be measured with radioactive saliva secreted by the parotid gland and submandibular glands. This saliva is adsorbed to the oral mucosa; thus, oral radioactivity indices can be considered practical indicators of overall salivary gland function. In the present study, the trial group maintained significantly better oral indices at the prestimulatory ($P = .01$) and poststimulatory ($P = .009$) stages at 1 month post-RT as compared with the control group, suggesting that supplementation of vitamin C/E complex protected salivary gland function against RT-induced damage.

The major limitation of this study was the incompleteness of the salivary scintigraphy data (in the control and trial groups, 16 of 26 patients completed scintigraphy at all 3 time points). Subjects receiving RT complained of severe difficulties and discomfort during scintigraphy, worse than initially expected. Specifically, some patients could not hold the sialogogue (lemon juice) long enough to stimulate the salivary gland sufficiently. Also, patients were required to stand for lengthy periods during scintigraphy (average, 40-50 minutes). Unfortunately, we did not find an adequate substitute instrument for scintigraphy during the trial. This highlights the necessity of developing more convenient methods of quantifying salivary function in patients undergoing cancer treatment. Another limitation was that salivary function was not assessed after 6 months. This makes it difficult to determine whether short-term supplementation with vitamin C/E complex during RT has a long-term impact on salivary function.

Taken together, our data support the hypothesis that short-term, low-dose vitamin C/E complex supplementation during RT contributes to preservation of salivary gland function in patients with HNC, and therefore to relief of patient discomfort due to RT-induced xerostomia.

**Author Contributions**

**Man Ki Chung**, substantial contributions to the conception or design of the work, interpretation of data for the work, drafting the work critically for important intellectual content, final approval of the version to be published, accountability for all aspects of the work; **Do Hun Kim**, substantial contributions to the conception or design of the work, interpretation of data for the work, drafting the work critically for important intellectual content, final approval of the version to be published, accountability for all aspects of the work; **Yong Chan Ahn**, substantial contributions to the conception or design of the work, acquisition of data for the work, drafting the work critically for important intellectual content (salivary scintigraphy and image analysis part), final approval of the version to be published, accountability for all aspects of the work; **Eun Hye Kim**, acquisition of data for the work, drafting the work critically for important intellectual content (clinical trial protocol and follow-up part), final approval of the version to be published, accountability for all aspects of the work; **Young-Ik Son**, substantial contributions to the conception or design of the work, interpretation of data for the work, drafting the work critically for important intellectual content, final approval of the version to be published, accountability for all aspects of the work.

**Disclosures**

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**References**


