The Effect of Carbogen Breathing and Nicotinamide Added to Standard (Chemo)Radiation Treatment of Advanced Cervical Cancer in Indonesia

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Objective: Chemoradiation is the standard therapy for advanced stages of cervical cancer. In developing countries, where 80% of cervical cancers occur, this is not always available. Carbogen breathing and oral nicotinamide (CON) therapy, aimed at overcoming tumor hypoxia, has shown to improve treatment efficacy in some epithelial tumors. This study investigates the effect of CON during (chemo)radiation of advanced stages of cervical cancer on overall survival, local and regional control, and toxicity.

Methods: From December 2006 to February 2010, 139 patients with stage IB2 to IVA cervical cancer were nonrandomly assigned to receive radiotherapy (RT) or chemoradiation (CRT) with or without CON. Differences in overall survival, local and regional control after 1 year, and toxicity were assessed in 113 evaluable patients. Thirty-two patients received RT, 16 received CRT, 45 received CON-RT, and 20 received CON-CRT.

Results: The CON-RT and RT groups contained significantly more patients with a poor performance status and IIIB and IVA tumors. Despite these differences in baseline characteristics, overall survival and local and regional control at 1 year were not significantly different ($P = 0.10$ and $P = 0.19$, respectively). Toxicity scores also did not differ ($P = 0.60$ and $P = 0.73$ for acute and late toxicity).

Conclusions: Addition of CON to standard (chemo)radiation gives comparable survival and control rates. The effect of CON might be underestimated due to differences in baseline characteristics. Because chemotherapy cannot always be (completely) administered in low-resource settings, CON could be a worthy substitute. The CON treatment is feasible and safe.

Key Words: Oxygen modification, Radiotherapy, Chemotherapy, Cervical cancer

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Cervical cancer is the second most common type of cancer (17.8 per 100,000) and cause of cancer deaths (9.8 per 100,000) among women aged 15 to 44 years in developing countries. In Indonesia, a low-middle income country in Southeast Asia with a population estimated at 248 million inhabitants, cervical cancer is the third most common type of cancer (12.8 per 100,000) and fourth most common cause of death due to cancer (7.0 per 100,000) in women. In Cipto Mangunkusumo Hospital, cervical cancer is the most prevalent gynecologic cancer and has a mortality rate of 66.1%.

A cervical cancer screening program has been widely introduced in Indonesia. However, the public awareness of the importance of this program is limited. As a result, cervical cancer is often found at an advanced stage of disease. Optimal treatment for advanced stages consists of a combination of radiotherapy (RT) and cisplatinum-based chemotherapy. Chemotherapy, however, is not always available or is not administered because of medical reasons.

The efficacy of RT in cervical cancer treatment is limited by hypoxia within the tumor. Studies have shown that hypoxia is an independent predictor of survival in cervical cancer. Carbogen breathing and oral nicotinamide (CON) therapy, a combination of carbogen and nicotinamide, has been shown to reduce tumor hypoxia. Carbogen is a mixture of 98% oxygen and 2% carbon dioxide, which increases partial oxygen pressure, thereby reducing chronic hypoxia seen especially around necrotic tissue at the diffusion distance of oxygen. Nicotinamide is a vasodilator preventing intermittent closure of blood vessels, thereby reducing acute hypoxia. Carbogen breathing and oral nicotinamide therapy has been shown to improve survival and regional control in squamous cell carcinoma of the larynx and survival in transitional cell bladder cancer.

Carbogen breathing can be achieved by breathing through a scuba diving mask during RT. Nicotinamide is administered orally before each RT session via fruit juice. The CON therapy therefore is cheap and easy to administer. This makes CON very suitable for countries with limited resources. This study investigates the effect of CON during radiation therapy in advanced-stage cervical cancer on overall survival, local and regional control, and toxicity in Jakarta, Indonesia.

PATIENTS AND METHODS

A prospective study was performed in Dr Cipto Mangunkusumo Hospital, Jakarta, a government-funded hospital and the national referral center in Indonesia, from 2006 until 2010. Carbogen breathing and oral nicotinamide was offered to patients who were planned to undergo (chemo)radiation for advanced-stage (stage IB2-IVA) cervical cancer.

Inclusion Criteria

The inclusion criteria are as follows:

- Histologically confirmed squamous cell or adenocarcinoma of the cervix
- Clinical stages IB2, IIA, IIB, IIIA, IIIB, or IVA
- Able to understand the study protocol and consent to it
- Older than 18 years

Exclusion Criteria

The exclusion criteria are as follows:

- No prior or concurrent treatment for this tumor
- No prior or concurrent other malignancy during the previous 5 years except basal cell carcinoma of the skin or superficial bladder neoplasm (pTa)
- Eligibility for the study was assessed by a team of gynecologists and radiotherapists.

Although implementing the study, chemotherapy became available to all patients with advanced stages of cervical cancer in Indonesia. Chemoradiation therefore became the standard therapy for patients who were physically fit. These patients were categorized as having a good performance status. Patients unfit to receive chemotherapy (due to poor general condition and/or renal failure) were categorized as having a poor performance status. Those patients were excluded from chemotherapy and selected for RT alone (Table 1, Supplemental Digital Content 1, http://links.lww.com/IGC/A233). In this way, patients in the chemoradiation (CRT) groups all had a good performance status, whereas patients in the radiation groups either had a poor performance status or a good performance status if other reasons for not selecting chemotherapy treatment existed (eg, patients consent). After the selection for either CRT or RT, patients were nonrandomly assigned to receive CON. Thus, 4 treatment groups were formed as follows: CON-CRT group, CRT group, CON-RT group, and RT group.

Primary and Secondary Outcomes

The primary end point was overall survival defined as time to death due to all causes after completing treatment. Secondary end points were local and regional cancer control and treatment toxicity. Local and regional control was defined as time to local or regional tumor recurrence or tumor progression after incomplete response. A tumor residue was defined as the presence of tumor up to 6 months after finalizing treatment. From 6 months onwards, the occurrence of a local tumor was categorized as tumor recurrence. This was done because we anticipated some difficulty in assuring adequate follow-up. Toxicity was measured with the National Cancer Institute Common Toxicity Criteria version 2.0 and the acute and late morbidity scales of SOMA Lente for RT.

Diagnostic Workup and Treatment

Diagnostic workup comprised the patient’s full history and physical examination, including a gynecologic examination with visual and manual confirmation of the tumor. Furthermore, tumor biopsy was performed for histological confirmation of the cervical cancer. A computed tomography (CT) scan was not standard in the pretreatment workup because of costs and limited availability.

Radiotherapy

After diagnosis, all patients were treated with RT consisting of both external beam radiation therapy and brachytherapy. External beam therapy was delivered by megavoltage photon beam with a linear accelerator or cobalt-60 machine and consisted of 5 weeks of 5 sessions a week with 2-Gy fractions,
preceded by a simulator session to determine radiation fields. A CT scan was performed to mark the radiation field and its borders. The cranial border was at L4 to L5; the caudal border was at the ramus inferior of the os pubic or 2 cm from the distal end of the tumor. The lateral borders were 2 cm lateral of the innominate linea, with a minimal margin to the tumor of 2 cm. The anterior border was the inferior border of the symphysis pubic, and the posterior border was the sacrum.

Brachytherapy consisted of 3 once-a-week sessions of 7 Gy or 2 once-a-week sessions of 8.5 Gy using a Fletcher application. The reference point for brachytherapy was point A. Total standard treatment time was 8 weeks.

**CON Therapy**

Carbon breathing was started 4 minutes before radiation therapy and was continued throughout radiation using a scuba diver breathing regulator. Details of this breathing system have been described before. Nicotinamide (60 mg/kg with a maximum of 6 g) was dissolved in fruit juice and administered orally 1 hour before irradiation. To prevent nausea, domperidon 10 mg 3 times a day was given during the complete duration of treatment.

**Chemotherapy**

Chemotherapy consisted of 40 mg/m\(^2\) cisplatinum weekly for 5 weeks during external beam radiation. It proved that it is very difficult to deliver all 5 courses of chemotherapy; therefore, we deemed a total of 3 or more courses of chemotherapy to be a complete treatment.

During treatment, patients had weekly checkups, with a history and physical examination. Hemoglobin, hematocrit, creatinine, and urea levels were checked twice weekly. From the finish of treatment onwards, patients were planned to be seen every 3 months in the first 2 years, every 6 months in the next 2 years, and every year thereafter. General physical and gynecological examination was then performed. During the first and second follow-up visit, a cervical biopsy or smear was performed to assess treatment response. During further follow-up, biopsies were only taken if indicated by complaints or suspicious areas during examination.

**Data Collection**

Available data were entered into the study database. This included patient characteristics as well as tumor type and

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**TABLE 1. Demographics according to treatment group**

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>CRT</th>
<th>CON-RT</th>
<th>CON-CRT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>32 (28)</td>
<td>16 (14)</td>
<td>45 (40)</td>
<td>20 (18)</td>
<td>0.50</td>
</tr>
<tr>
<td>Age, y</td>
<td>Median</td>
<td>48</td>
<td>51</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>34–72</td>
<td>33–67</td>
<td>32–70</td>
<td>36–64</td>
</tr>
<tr>
<td>Stage</td>
<td>IB2-IIB</td>
<td>8 (25)</td>
<td>7 (44)</td>
<td>9 (20)</td>
<td>10 (50)</td>
</tr>
<tr>
<td></td>
<td>IIIB-IVA</td>
<td>24 (75)</td>
<td>9 (56)</td>
<td>36 (80)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Well</td>
<td>4 (13)</td>
<td>3 (19)</td>
<td>8 (18)</td>
<td>5 (25)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>18 (56)</td>
<td>9 (56)</td>
<td>24 (53)</td>
<td>9 (45)</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>5 (16)</td>
<td>2 (13)</td>
<td>9 (20)</td>
<td>5 (25)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>5 (16)</td>
<td>2 (13)</td>
<td>4 (9)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Tumor volume, cm(^3)</td>
<td>0–60</td>
<td>13 (41)</td>
<td>8 (50)</td>
<td>25 (56)</td>
<td>11 (55)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>19 (59)</td>
<td>8 (50)</td>
<td>20 (44)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Performance status</td>
<td>Good</td>
<td>23 (74)</td>
<td>16 (100)</td>
<td>24 (53)</td>
<td>20 (100)</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>9 (28)</td>
<td>0 (0)</td>
<td>21 (47)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total treatment time</td>
<td>Median</td>
<td>75</td>
<td>75</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2–251</td>
<td>43–96</td>
<td>15–158</td>
<td>50–84</td>
</tr>
<tr>
<td>Follow-up days</td>
<td>Median</td>
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<td>515</td>
<td>402</td>
<td>443</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>13–1187</td>
<td>83–1354</td>
<td>58–2115</td>
<td>122–1453</td>
</tr>
</tbody>
</table>

*P value of overall comparison was set in boldface. Values were presented as n (%).

*P value of comparison according to treatment with or without CON.

†P value of comparison according to treatment with or without chemotherapy.
tumor stage. The performance status was based on the type of treatment and, if applicable, the reason for not giving chemotherapy. Finally, toxicity data and follow-up data were entered into the database.

Follow-up was initially poor, so this was intensified by calling patients, sending letters, and even visiting patients at their homes. Home visits were preferably followed by a checkup at the RT department. During the checkup, a full history and physical examination was performed. As a stimulus to come for a visit, patients were offered a financial compensation of travel expenses.

The available data were reviewed by 2 separate investigators (W.J.M.W. and R.L.M.B.) to confirm outcome in all cases.

Data Analysis
Statistical analysis of the data was performed using SPSS version 19 (IBM, Chicago, IL).

Differences in baseline characteristics and acute and late toxicity were calculated using the analysis of variance test and the $\chi^2$ test. Survival estimates were calculated using the Kaplan-Meier method. Differences were compared using the log-rank test. $P \leq 0.05$ (2-sided) was deemed significant.

RESULTS
Between December 2006 and February 2010, 134 cases were included in the study. Although reviewing the database, in 12 cases, treatment was unclear. Five had no RT department medical record, and 7 others had no gynecology department record; however, the RT record was not conclusive on the type of treatment given.

As shown in Supplemental Digital Content Table 1 (http://links.lww.com/IGC/A233), 9 other cases were lost to follow-up, meaning that they did not show up for any consultation after completion of treatment and that they could not be reached by phone or regular mail. All other cases had at least 1 consultation at the gynecology or RT department after treatment. One hundred thirteen cases were eligible for analysis.

Data Collection
Calling patients at home proved to be an effective measure of updating follow-up as in 64 cases where extra information was collected. In further 9 cases, updated information was collected through home visits. Of these 73 cases, 17 (23%) came for a consultation to the RT department. Sixteen others (22%) were still regularly checked by the gynecologist; 14 (19%) lived outside Jakarta and were either not able to come to the hospital or had regular checks in other hospitals in Indonesia. Only 1 patient found the reimbursement for travel expenses too low to come to the hospital.

Protocol Violations
Radiotherapy was incomplete in a total of 12 cases (11%). Nine received RT, whereas 3 others received CON and RT.

In 5 cases, external beam RT (EBRT) was not completed (2 because of financial problems, 1 because of a bladder metastasis after 2 EBRT sessions, and 1 could not handle the combination of CON and RT), but this became clear only at a follow-up phone call months after treatment. In 1 other case, the reason was unclear.

Three patients stopped RT treatment between EBRT and brachytherapy. One was in bad condition and died of tuberculosis shortly afterwards; 2 others had unclear reasons for stopping. They were both in the RT-only group.

Four patients had 2 rounds of brachytherapy but failed to receive the final round. One developed a distant metastasis at that time, whereas the other 3 had unclear reasons for discontinuing treatment. Of these 3, one was treated with CON-RT, the others had RT. The CON therapy was generally well tolerated (overall compliance rate of 89%). Four patients discontinued CON without stopping RT (3 because of vomiting, 1 because of a deteriorating renal function).
Chemotherapy was started in 69 patients, but only 4 patients received the scheduled 5 doses. In total, 36 patients received at least 3 doses of chemotherapy and were reported in the groups CRT (n = 16) and CON-CRT (n = 20). Thirty-three patients received 1 or 2 doses of chemotherapy and were reported in the groups RT (n = 16) and CON-RT (n = 17). The most important reason for discontinuing chemotherapy was onset of renal failure that was absent at the start of chemotherapy (n = 13, 39%). Hydronephrosis can explain the high number of renal failure because there was stage IIIB cervical cancer in 9 cases and stage IIB in 4 cases. In all other cases, the cause remains unknown.

Demographics

As shown in Table 1, patients’ demographics differed significantly on performance status and stage. Patients with a poor performance status, as well as most patients with stage IIIB or IVA, were found in the groups not receiving chemotherapy (P = 0.01 and P ≤ 0.001, respectively).

Primary Outcome

The overall survival by tumor stage is shown in Figure 1A. As expected, survival decreased from stage IB2 to IIIB. One-year survival was 100% in stage IB2 and is 81% in stage IIIB.

Figure 1B shows the overall survival according to treatment modality. The CON therapy did not show an improvement of overall survival after 1 year as shown by the comparison of RT versus CON-RT (87% vs 71%; P = 0.58) and CRT versus CON-CRT (88% vs 79%; P = 0.79).

Chemotherapy had no significant positive effect on 1-year overall survival either (RT vs CRT; 87% vs 89%) and CON-RT versus CON-CRT (74% vs 88%; P = 0.06), but the 3-year overall survival of CRT was significantly better than in RT (44% vs 59%; P = 0.05).

![FIGURE 2. A, Overall survival in patients with good performance status according to treatment, B, Overall survival in patients with good performance status according to treatment with or without CON, C, Overall survival in patients with good performance status according to treatment with or without chemotherapy.](image)

![FIGURE 3. A, Local/regional control of all patients according to treatment, B, Local/regional control of all patients according to treatment with or without CON, C, Local/regional control of all patients according to treatment with chemotherapy.](image)
After selecting patients with a good performance status (Fig. 2), there was no significant difference in overall survival between the groups regarding the addition of CON and the addition of chemotherapy.

Secondary Outcome

Local and regional control analyses yielded no significant results after 1 year as shown in Figure 3 ($P = 0.19$). Neither chemotherapy nor CON therapy did have a significant impact on local and regional control after 1 year. Interestingly, the local and regional control rates were much higher than the overall survival rates. This indicates that many of the patients entered in this study had comorbidities related (eg, distant metastases in unrecognized stage IVB) or unrelated to the tumor. That could have resulted in a bias to treatment allocation. The performance status was introduced to limit allocation bias. Therefore, the local and regional control rate in patients with a good performance status is best suited to illustrate the effect of adding chemotherapy and/or CON to RT without this bias (Fig. 4). Local and regional control curves did differ in favor of addition of CON and chemotherapy, especially after the first year of follow-up, but differences are nonsignificant ($P = 0.56$ and $P = 0.25$, respectively).

Toxicity

As shown in Table 2, most patients (89%) reported self-limiting (grade 1 or 2) acute toxicity effects (most often abdominal discomfort, nausea, diarrhea, and moderate mucositis). Non–self-limiting toxicity effects (grade 3–4) were only seen in CON-RT and RT patients ($n = 5$), who were most vulnerable. In 4 patients, complaints stopped after the completion of treatment. One patient died due to hypoalbuminemia secondary to radiation colitis.

Late toxicity was seen in 21% of cases. Three patients experienced severe toxicity effects. One patient died of radiation

| TABLE 2. Acute and late toxicity according to treatment group |
|---------------------------------|----------------|----------------|----------------|----------------|-------|
|                                | RT             | CRT            | CON-RT         | CON-RT         | $P$   |
| Acute toxicity                 |                |                |                |                |       |
| No toxicity                    | 4 (13)         | 1 (6)          | 2 (4)          | 1 (5)          | 0.60  |
| Grade 1–2                      | 26 (81)        | 15 (94)        | 40 (89)        | 19 (95)        | 0.49* |
| Grade 3–4                      | 2 (6)          | 0 (0)          | 3 (7)          | 0 (0)          | 0.26† |
| Late toxicity                  |                |                |                |                |       |
| No toxicity                    | 26 (81)        | 11 (69)        | 35 (78)        | 17 (85)        | 0.73  |
| Grade 1–2                      | 6 (19)         | 4 (25)         | 9 (20)         | 2 (10)         | 0.84* |
| Grade 3–4                      | 0 (0)          | 1 (6)          | 1 (2)          | 1 (5)          | 0.41† |

$P$ value of overall comparison was set in boldface. Values were presented as $n$ (%).

* $P$ value of comparison according to treatment with or without CON.

† $P$ value of comparison according to treatment with and without chemotherapy.
colitis, another had a perforated sigmoid for which a colostomy was inserted, whereas a third patient had a vesicovaginal fistula without a tumor recurrence or residue.

The CON therapy did not cause significantly more toxicity effects. Evaluating the toxicity of chemotherapy was difficult because it is not known whether patients did not complete chemotherapy treatment because of toxicity effects. The registered toxicity effects did not show an increase in toxicity effects in chemotherapy groups.

**DISCUSSION**

This is the first study to report on the addition of CON in a large number of patients with advanced-stage cervical cancer. This study shows that in the setting of a limited resource country, the addition of CON to (chemo)radiation does not significantly improve the overall 1-year survival in advanced-stage cervical cancer. However, further analysis shows that there seems to be an effect of CON on local and regional control beyond 1 year of follow-up and that the effect on overall survival might be masked due to comorbidities and understaging, influencing treatment allocation. This study also shows that the addition of chemotherapy to RT does improve overall survival; however, this may be an overestimation due to patient selection.

Other studies have shown that CON addition to RT in epithelial tumors improves overall survival and local and regional control.10,11 These studies were performed in high-income countries with excellent staging facilities and well-controlled circumstances, making follow-up easier. Cervical cancer, however, is becoming rare in developed countries, and large-scale clinical studies in advanced-stage disease become impossible due to a lack of patients. So, further study is necessary to confirm the effect of CON therapy on cervical cancer control, but patient selection must be firm, treatment allocation must be strictly randomized, and follow-up must be solid. In that setting, we expect CON therapy to have a positive effect on both survival and local and regional control, without increased toxicity. Carbogen breathing and oral nicotinamide could even be an alternative to chemotherapy when this is unavailable or incomplete chemotherapy treatment is anticipated.

Certain major limitations in this study exist, as indicated earlier. These can be primarily attributed to logistic problems associated with research and clinical care in a low-resource country, but it also reflects the standard of care in Indonesia. First, staging of patients was done in an outpatient setting without additional CT or MRI scan. This may have caused understaging in this patient group and inclusion of patients with stage IVB disease, which may have masked any effect of the intervention on overall survival. Second, the allocation between treatment groups was not performed according to standard. This resulted in crossover treatment, which additionally was not documented well, so original treatment allocation could not be retrieved leading to nonrandom allocation to the intervention. Furthermore, adherence to treatment protocol was difficult because of logistic problems. As a result, most patients had a treatment time of more than 8 weeks. In addition, many patients that started with CRT only received chemotherapy once or twice. This might have obscured the effect of CON, as we did find a significant effect of chemotherapy on the outcome parameters. Finally, assessing follow-up proved to be difficult as many patients came from afar and did not return for follow-up, moved to different addresses, or changed phone numbers. As a result, follow-up was often scattered or incomplete and may have been biased toward patients that lived in the Jakarta region and toward patients with complaints or recurrences as they were more likely to return.

Despite these limitations, this study is, to our knowledge, the first study that examines the effect of CON therapy in cervical cancer and is the first study to report on survival of advanced-stage cervical cancer patients in Indonesia. Interestingly, despite hampered adherence to international protocols, overall survival for stage IIB tumors in Indonesia after 1 and 2 years correlates with rates in Western countries.15

In conclusion, this study shows that with the addition of CON to (chemo)radiation in advanced-stage cervical cancer, patients may have a positive effect on local and regional control and possibly even on overall survival. However, this needs to be confirmed in a randomized controlled trial. In addition, this study has shown that the application of CON is easy to implement, even in a low-resource setting and even in patients not able to receive chemotherapy. We think CON deserves further study in the treatment of advanced-stage cervical cancer in low-resource countries.

**REFERENCES**


