Tongue cancer during pregnancy: Surgery and more, a multidisciplinary challenge

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1. Introduction
2. Material and methods
2.1. Patient 1
2.2. Patient 2
2.3. Patient 3
2.4. Patient 4
2.5. Patient 5
2.6. Patient 6
3. Discussion
3.1. The Surgeon’s point of view
3.2. The Anesthesiologist’s point of view
3.3. The Radiation Oncologist’s point of view
3.4. The Medical Oncologist’s point of view
3.5. The Obstetrician-Gynecologist’s point of view
3.6. The Obstetrician-Gynecologist’s point of view
3.7. General considerations
4. Conclusions
Conflict of interest
Acknowledgment
References
Biographies

Abstract
No international guidelines are available for the treatment of oral tongue cancer during pregnancy. Six patients with tongue cancer during pregnancy were identified by a retrospective chart review. In three of the cases we did not follow the standard treatment, the women had disease progression, and two of them died after a short time.

A multidisciplinary discussion and literature review suggest that following the standard surgical procedure could be the optimal treatment to ensure mother and baby health in tongue cancer. Nonetheless choosing between maternal advantage and potential fetal damage should not be an individual medical decision. Treatment "customization" is a possibility. Patients and their families should be provided with comprehensive information and appropriate support in order to fully participate in the decision-making process. The patient's care may be improved if carried out in a specialized maternity center where the surgical oncologic treatment is managed together with the obstetric aspects.

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1. Introduction

Cancer is the second most common cause of death during the reproductive years in the United States (Jemal et al., 2010; Jemal et al., 2009). In Italy, the estimated number of new cases of cancer in women below the age of 40 is 9410 per year, with a crude incidence rate of 94.5/100,000 (Wingo et al., 1995). Even though the incidence of cancer during pregnancy is relatively low, accounting for 0.02–0.1% of all pregnancies (United Nations data retrieval system, 2012; Weisz et al., 2001; Koren et al., 2005; Pentheduval et al., 2009), this figure is expected to increase, mainly as a result of the consistent trend to postpone pregnancy to the fourth decade, when the cancer incidence is higher (Byers, 1975; Schantz and Vu, 2002).

Breast (46%) and hematological cancers (18%) are the most frequently diagnosed oncologic diseases during pregnancy, while oral cancers are rare and account for only 25 of all gestational cancers (Van Calsteren et al., 2010; Lloyd et al., 2003).

The overall incidence of oral tongue carcinoma in young patients has recently increased, especially in young Caucasian women between 18 and 44 years of age (Park et al., 2010). This increase does not seem to be associated with the usual risk factors such as alcohol, tobacco and marijuana. Human papilloma virus (HPV) infection could be possibly related, but the role of this virus in oral tongue cancer is not so evident as in oropharyngeal and base of tongue cancers (Attner et al., 2010; Combes and Franceschini, 2014; Chung et al., 2014; Smith et al., 2004). Moreover, it has been hypothesized that the hormonally-induced changes of pregnancy may promote squamous epithelial proliferation, but it has not yet been determined whether there exists a biological predisposition to head and neck squamous cell carcinoma (HNSSC) during pregnancy (Eliasson et al., 2013).

According to the current National Comprehensive Cancer Network (NCCN) guidelines, organ-preserving surgery or radiotherapy are indicated as first line treatment in early-stage oral cancers (Chung et al., 2014). For advanced cases, radical surgery followed by postoperative radiotherapy or combined chemo-radiation is the accepted multimodality treatment (National Comprehensive Cancer Network, 2013; Klug et al., 2008; Robbins et al., 2004; Amba et al., 2010a; Mhalleem Gziri et al., 2013; Yokoshina et al., 2012).

When oral tongue cancer is diagnosed in a pregnant woman, both clinician and patient are faced with the unique challenge of balancing maternal and fetal health. Although early detection and effective management are key to successful treatment, it is of paramount importance to weigh the fetal risks with the possible maternal advantages (Eliasson et al., 2013). Choosing suboptimal treatment in order to preserve the fetal health is never the best choice, as this may worsen maternal outcome, but it may be considered if the mother requests it (Weisz et al., 2001; Mhalleem Gziri et al., 2013; Lasansis and van der Mark, 1996; Avolio and Patrick, 2000).

Treatment protocols for patients with oral tongue cancer during pregnancy should consider tumor, fetal and patient factors. Tumor-specific factors comprise histologic type, site, stage, and perineural or vascular invasion (Lasansis et al., 1996; Arato and Patrick, 2008; Llewellyn et al., 2001); fetal-specific factors include gestational age at diagnosis, fetal growth rate, and expected weight at birth; patient-specific factors comprise maternal conditions, nutritional status, co-morbidities and the mother’s wish concerning whether to continue or to interrupt the ongoing pregnancy (Patrick and Raghaaon, 2004; Moran et al., 2007).

In this paper, we report our experience in treating oral tongue cancer diagnosed during pregnancy and we discuss this issue within the framework of a multidisciplinary approach, with the points of view of the surgeon, the anesthesiologist, the radiation therapist, the medical oncologist, the neonatologist and the obstetrician-gynecologist.

2. Material and methods

Six patients with a diagnosis of tongue cancer during pregnancy were identified by means of a retrospective chart review. Patients were treated in the Division of Head and Neck Surgery of the European Institute of Oncology (IEO), in the Division of Otolaryngology of the Policlinico of Milan and in the University Department of Odontostomatological Diseases, Policlinico of Bari from 1986 to 2011. Age at diagnosis, gestational age, type of tumor, type of treatment, adverse events and maternal and neonatal outcome are reported in Table 1.

2.1. Patient 1

A 31-year-old, 15 weeks pregnant woman was referred with a cT1N0M0 squamous cell carcinoma (SCC) of the tongue in June 1986. The lesion was 2 cm diameter and involved the anterior third of the tongue. Her previous medical history was unremarkable. The patient underwent trans-oral wide excision of the lesion one month after diagnosis. The pathologic specimen revealed a well-differentiated SCC, with surgically-negative tumor margins (pT1N0M0). The patient delivered at term and the baby developed normally, with unremarkable medical history. After 28 years of follow-up, the patient is alive and free of disease.

2.2. Patient 2

A 35-year-old, 22 weeks pregnant woman was referred with a cT1N0M0 SCC of the tongue in June 1992. The lesion measured roughly 1.5 cm and involved the right margin of the tongue. Her medical history was negative for concomitant diseases. At 26 weeks gestation she underwent trans-oral wide excision of the lesion and the pathologic specimen revealed a well-differentiated SCC with a 2 mm invasion depth. All tumor margins were negative (pT1N0M0). The patient delivered at term and the baby developed normally. After 18 years of follow-up, the patient remains free of disease and in good health.

2.3. Patient 3

A 30-year-old, 11 weeks pregnant woman was referred with a cT1N0M0 SCC of the tongue in March 2002. The lesion measured roughly 2 cm and was in the left margin of the tongue. No relevant comorbidities. At 15 gestational weeks, the patient underwent trans-oral wide excision of the lesion, with a pathologic specimen revealing a well-differentiated SCC with negative margins (pT1N0M0). The child was delivered at term and developed normally. The patient is currently free of disease.
Table 1
Patients characteristics, treatment, maternal and fetal outcome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>pTNM classification</th>
<th>Smoking</th>
<th>Gestational age at diagnosis weeks</th>
<th>Treatment during pregnancy/ Fetal outcome</th>
<th>Maternal outcome</th>
<th>Treatment after pregnancy</th>
<th>pTNM classification</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>SCC on anterior one-third</td>
<td>pt1cN0M0</td>
<td>No</td>
<td>19</td>
<td>Trans-Oral wide excision Delivery at 38 wks of healthy baby</td>
<td>Alive with no evidence of disease (NED)</td>
<td>No</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>#2</td>
<td>SCC on the right margin</td>
<td>pt1cN0M0</td>
<td>No</td>
<td>26</td>
<td>Trans-Oral wide excision Delivery at 40 wks of healthy baby</td>
<td>NED</td>
<td>No</td>
<td>/</td>
<td>NED Completed standard oncologic 5-years follow up</td>
</tr>
<tr>
<td>#3</td>
<td>SCC on the left margin</td>
<td>pt1cN0M0</td>
<td>No</td>
<td>15</td>
<td>Trans-Oral wide excision Delivery at 38 wks of healthy baby</td>
<td>NED</td>
<td>No</td>
<td>/</td>
<td>NED Completed standard oncologic 5-years follow up</td>
</tr>
<tr>
<td>#4</td>
<td>SCC on the right margin</td>
<td>pt1cN0M0</td>
<td>No</td>
<td>11</td>
<td>Partial glossectomy Delivery at 34 wks of healthy baby</td>
<td>NED</td>
<td>No</td>
<td>/</td>
<td>NED Completed standard oncologic 5-years follow up</td>
</tr>
<tr>
<td>#5</td>
<td>SCC on the right margin</td>
<td>ypT4aN0M0</td>
<td>No</td>
<td>24</td>
<td>Delivery at 34 weeks of a baby with a respiratory distress syndrome, discharged in good health at 35 days of life</td>
<td>NED</td>
<td>No</td>
<td>/</td>
<td>NED Completed standard oncologic 5-years follow up</td>
</tr>
<tr>
<td>#6</td>
<td>SCC on the right margin</td>
<td>ypT1N0M0</td>
<td>No</td>
<td>28</td>
<td>Partial glossectomy Delivery at 34 wks of healthy baby</td>
<td>NED</td>
<td>No</td>
<td>/</td>
<td>NED Completed standard oncologic 5-years follow up</td>
</tr>
</tbody>
</table>

NED = alive with no evidence of disease; DDO = dead of disease.

2.4. Patient 4

A 32-year-old woman was referred with a cT2N0M0 SCC of the tongue in August 2009 at 24 weeks of gestation. The lesion measured 2.5 cm and was vegetating through the anterior left side of the tongue. It was painful and ulcerated. It extended to the floor of the mouth, but no palpable lymph nodes were detected. At 28 weeks of pregnancy, she underwent left partial glossectomy. The pathologic specimen revealed a well-differentiated SCC of the left side of the tongue, 2 cm maximum diameter, with a depth of invasion of 4 mm and negative tumor margins (pt1cN0M0). A prophylactic lateral neck dissection was not performed, but monthly follow-up by neck ultrasound (US) was planned (Shah and Gil, 2009; Calabrese et al., 2009, 2011, 2013). At 32 weeks gestation, the patient noted a lateral neck lymph node of 2-5 cm. At 34 weeks a healthy baby was delivered by cesarean section and two weeks later the patient underwent selective left lateral neck dissection (level I-V). A single node metastasis with extra capsular spread (ypT0pN2aN0M0) was found in region II. The patient completed treatment with chemoradiotherapy following standard protocols. At present, she is free of disease.

2.5. Patient 5

A 37-year-old woman with a recent history of excisional biopsy of a well-differentiated SCC on the right side of the tongue was referred in March 2010. She was 26 weeks pregnant and at physical examination had a tender, vegetative, infiltrative area measuring approximately 4 cm in the posterior half of the right side of the tongue. There was a clinically apparent involvement of the right extrinsic muscles, but no palpable lymph node on both sides of the neck (ypT4aN0M0). A preterm cesarean section was planned and the patient delivered a healthy female infant at 30 weeks gestation. The baby was intubated and recovered in the neonatal intensive care unit, and was discharged after 35 days in good condition. One week after delivery, the patient underwent major surgery; right partial glossectomy with mandibulectomy, local reconstruction with anterolateral thigh free flap and right functional selective neck dissection (I-V). The pathologic specimen revealed a moderately differentiated SCC of the right side of the tongue (pt4aN0M0) with negative tumor margins. The post-operative course was complicated by anterolateral thigh flap ischemia, possibly related to microvascular thrombosis. The flap was replaced by a pectoralis major flap, but the post-operative course was again complicated
with wound dehiscence, local tissue suffering, partial flap necrosis due to vasculitis, and salivary fistula. The patient developed a depressive syndrome and she did not accept any further treatment (postoperative radiotherapy according to international guidelines). She died after two years from extensive liver and pulmonary metastases.

### 2.6 Patient 6

A 40 year-old woman was referred on May 2012, she had an oncological history of moderately differentiated SCC of the tongue diagnosed during her previous pregnancy in December 2010. She was 12 weeks pregnant and had a thick and ulcerated lesion in the right middle third of the tongue. The lesion was extending to the floor of the mouth (ypT1N0Mo). She was a former smoker, but had no previous history of alcohol intake. The patient underwent trans-oral partial glossectomy at the 14th week of gestation, and the pathologic specimen revealed a 1 cm moderately differentiated, ulcerated SCC with a depth of invasion of 4 mm with negative tumor margins (ypT1cN0M0). We decided not to perform prophylactic lateral neck dissection and instead to follow up the patient with monthly neck US (Shah and Gil, 2009; Calabrese et al., 2009, 2011, 2013). At the time of the planned delivery at 34 weeks, the patient noted a lateral neck lymph node. The cesarean section was uneventful, and two weeks after delivery she underwent selective lateral neck dissection (level I-V). Metastases were found in three lymph nodes, with extra-capsular spread (ypT0P0N2bM0). After surgery, the patient completed treatment with chemoradiotherapy, according to standard protocols. The patient relapsed in the lungs and mediastinal nodes 6 months after the conclusion of chemoradiotherapy and died four months later.

### 3. Discussion

In our series we describe five pregnant patients with early stage SCC of the tongue treated with simple surgery (three patients - #1, #2 and #3 - with a wide excision; two patients - #4 and #6 - with partial glossectomy) and one case - #5 - of a locally advanced SCC treated with complex major surgery: partial glossectomy with mandibulotomy, unilateral selective neck dissection and antero-lateral thigh free flap reconstruction.

The median age at diagnosis was 34 years (range 30–40 years) and all patients were referred after the first trimester of pregnancy. We can divide our patients into 3 groups:

The first group (patients #1, #2 and #3) had a pT1cN0M0 tumor and underwent wide excision of the tongue during pregnancy. Tumor thickness was less than 3 mm; therefore homolateral neck dissection was not performed (Lewellyn et al., 2001). All patients are still alive, and show no evidence of disease; nor did they have any post-operative or obstetrical issues.

The second group includes cases #4 and #6. Both patients had a tumor thickness of 4 mm at pathologic specimen sampling. Nevertheless, we did not perform prophylactic lateral neck dissection for fear of fetal morbidity. Both patients had disease progression in the neck lymph nodes during their ongoing pregnancy and underwent radical neck dissection after delivery. They both received post-operative chemo-radiation; patient #6 died as a result of distant metastases, within one year from diagnosis.

The third group includes patient #5, a woman with advanced stage cancer who, according to clinical guidelines outside pregnancy, should have been treated with major surgery with flap reconstruction and postoperative radiotherapy. This surgery requires between 8 and 10h in the operating theatre so we decided not to perform such a demanding operation during pregnancy and to bring forward delivery as soon as possible. At 30 weeks gestational age, the patient delivered a baby who needed neonatal intensive care unit support. One week later the patient underwent major surgery with free-flap reconstruction. After surgery, she had repeated complications and refused any further post-operative treatment, dying 2 years after diagnosis.

#### 3.1. The Surgeon’s point of view

The surgical approach for cT1-2, cN0 tongue tumors includes a trans-oral tumor excision and a deferred lateral neck dissection 4 weeks after surgery, if the thickness of tumor infiltration turns out to be ≥ or = 3 mm at the definitive histological examination (Shah and Gil, 2009; Calabrese et al., 2009, 2011, 2013). All patients with clinical N1(N2a-c) tumors should undergo compartmental tongue surgery and receive post-operative combined radiotherapy +/- chemotherapy according to pathological findings. All patients with cT3-4 tumors, regardless of the clinical nodal status, undergo compartmental tongue surgery followed by radiotherapy +/- chemotherapy according to the histology. Conversely, all patients with cN3 undergo chemoradiotherapy and lateral neck dissection after the end of radiotherapy, in relation to residual tumor.

Compartmental tongue surgery means partial glossectomy, performed following anatomical structures, including the tumor nodes tract with an bloc lateral neck dissection and concomitant reconstruction with pedicled vs free flaps (Calabrese et al., 2009, 2011, 2013).

In pregnant women with tongue cancer, no guidelines are available; the literature suggests that pregnant women with tongue cancer should be treated as non-pregnant patients (Maliem Criet et al., 2013; Yokoshima et al., 2012), Table 2. This lack of evidence can lead to "individualized approaches” that may hamper clinical results.

#### 3.2. The Anesthesiologist’s point of view

During pregnancy, surgery for non-obstetric procedures occurs in up to 2% of women with a total number of procedures close to 75,000/year in Europe (Strong, 1990). Approximately 40% of these procedures occur in the first trimester, 35% during the second and 23% during the third (NI Muiuarechtagh and O’Gorman, 2006; Cohen, 1999). Acute abdominal problems are the most common clinical indications, followed by maternal trauma or malignancy. The outcome is generally favorable for both the mother and the fetus, but the physiological changes occurring during pregnancy should be considered, in order to preserve maternal and consequently placental tumor pressure (Reitman and Flood, 2011). Anesthetic drugs interfere with cell signal transmission, mitosis and DNA synthesis and may negatively affect fetal development, particularly when the fetus is exposed for a prolonged time (Van De Velde and De Buck, 2007; Kress, 1995; Langmoen et al., 1995; Cheek and Baird, 2009). Even though some animal studies have shown a teratogenic effect of nitrous oxide (N2O) and diazepam, no increased incidence of fetal malformations have been observed in humans (Van De Velde and De Buck, 2007; Cheek and Baird, 2009; Crawford and Lewis, 1986; Mazze and Kalén, 1989; Nejdlova and Johnson, 2012). Nonetheless, no sound data regarding operations with a duration greater than three hours are available. Pregnancy induces major alterations in human physiology. The earliest of these changes are hormonally-driven, while the later changes are related to the increasing uterine volume, increased metabolic demands and placental circulation (Nejdlova and Johnson, 2012). Reduction in functional residual capacity (FRC) and increased oxygen consumption (about 20% greater than non-pregnant women) can determine severe maternal hypoxia even after short periods of apnea (Van De Velde and De Buck, 2007; Cheek and Baird, 2009; Biro, 2011). Swelling
<table>
<thead>
<tr>
<th>Author Year</th>
<th>Tongue Cancer Case</th>
<th>Gestational age at diagnosis wks</th>
<th>pTNM classification</th>
<th>Treatment during pregnancy</th>
<th>Fetal outcome wk</th>
<th>Treatment after pregnancy or after pregnancy termination</th>
<th>Follow up yrs</th>
<th>Maternal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsworth et al. (2013)</td>
<td></td>
<td></td>
<td>T2N0M0 right</td>
<td>Neck dissection, mandibulectomy, partial glossectomy, and free flap reconstruction None</td>
<td>Delivery at 36 wk a HB</td>
<td>None</td>
<td>5</td>
<td>NED</td>
</tr>
<tr>
<td>Eikka et al. (2013)</td>
<td></td>
<td>First trimester</td>
<td>T4aN2aM0 right</td>
<td>Elective termination of pregnancy</td>
<td>Bilateral neck dissection, subtotal glossectomy and free flap reconstruction CT RT not concluded</td>
<td>1</td>
<td>Died from local recurrence and lung metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Last month</td>
<td>T2N2bM0 left</td>
<td>None</td>
<td>Delivery at 40 wk a HB</td>
<td>Neck dissection, partial glossectomy 1 month after delivery</td>
<td>12</td>
<td>NED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First trimester</td>
<td>T2N2bM0 left</td>
<td>Neck dissection, hemiglossectomy, Postoperative RT not performed None</td>
<td>Delivery at term</td>
<td>Neck dissection, right-sided resection of the tongue, floor of mouth and lateral mandible Postoperative RT NONE</td>
<td>12</td>
<td>NED</td>
</tr>
<tr>
<td>Yokoshima et al. (2012)</td>
<td></td>
<td>10</td>
<td>T3N0M0 right</td>
<td>Trans-Oral partial glossectomy Trans-Oral partial glossectomy</td>
<td>Delivery at 38 wk a HB</td>
<td>Delivery at 37 wk a HB Salvage surgery by neck dissection and subtotal glossectomy, free flap reconstruction Postoperative CT RT</td>
<td>3.6</td>
<td>NED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>T2N0M0 right</td>
<td>None</td>
<td>Delivery at 38 wk a HB</td>
<td>Trans-Oral partial glossectomy 1 month after delivery None</td>
<td>1</td>
<td>NED</td>
</tr>
<tr>
<td>Mhamede Garri et al. (2013)</td>
<td></td>
<td>24</td>
<td>T4N2bM0 left</td>
<td>Neck dissection and tumor excision Postoperative CT RT</td>
<td>Delivery at 38 wk a HB</td>
<td>None</td>
<td>6</td>
<td>NED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>T4N2aM0 left</td>
<td>Delivery at 36 wk a HB</td>
<td>Neck dissection</td>
<td>None</td>
<td>0.4</td>
<td>NED</td>
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<td>Author Year</td>
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<td>Gestational age at diagnosis (wks)</td>
<td>pTNM classification</td>
<td>Treatment during pregnancy</td>
<td>Fetal outcome (wk)</td>
<td>Treatment after pregnancy or after pregnancy termination</td>
<td>Follow up yrs</td>
<td>Maternal outcome</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>4 2000</td>
<td>2, 10</td>
<td>Tongue recurrence left</td>
<td></td>
<td>Tumor excision 1 wk after: hemiglossectomy and skin graft reconstruction</td>
<td>Delivery at 38 wk a HB</td>
<td>CT RT after third recurrence</td>
<td>1.5</td>
<td>NED</td>
</tr>
<tr>
<td>5 2005</td>
<td>5</td>
<td>Nodal recurrence during pregnancy (T2N2M0 left 1 yr before)</td>
<td></td>
<td>CT patient refused surgery</td>
<td>Delivery at 40 wk a HB</td>
<td>None</td>
<td>3.5</td>
<td>NED</td>
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<tr>
<td>Cheung et al. (2009)</td>
<td>1 25</td>
<td>T4N1M0 right</td>
<td></td>
<td>CT</td>
<td>Caesarean at 32 wk a HB</td>
<td>Concurrent CT RT and dissection for contralateral metastases</td>
<td>1.25</td>
<td>Died from local recurrence</td>
</tr>
<tr>
<td>Chow et al. (2006)</td>
<td>1 29</td>
<td>T2N0M0 right</td>
<td></td>
<td>Neck dissection, partial glossectomy and free flap reconstruction</td>
<td>Delivery at 38 wk a HB</td>
<td>NA</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>Akiko and Patrick (2008)</td>
<td>1 20</td>
<td>T2N2M0</td>
<td></td>
<td>Spontaneous abortion 27 wk</td>
<td>Caesarean at 32 wk a HB</td>
<td>Surgery and RT</td>
<td>1.3</td>
<td>Died</td>
</tr>
<tr>
<td>Tapsie et al. (2008)</td>
<td>1 31</td>
<td>T4N2aM0 dorsal</td>
<td></td>
<td>CT</td>
<td>Caesarean at 32 wk a HB</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Dumpee and Kerr (2005)</td>
<td>1 First trimester</td>
<td>Nodal recurrence during pregnancy (T2N2M0 left 2.5 yr before)</td>
<td></td>
<td>None</td>
<td>Elective termination of pregnancy</td>
<td>Neck dissection</td>
<td>6</td>
<td>NED</td>
</tr>
<tr>
<td>Kooi et al. (2005)</td>
<td>1 27</td>
<td>T3N2M0D left</td>
<td></td>
<td>None</td>
<td>Caesarean at 27 wk a HB</td>
<td>Intra-arterial infusion CT</td>
<td>2</td>
<td>Died for local recurrence</td>
</tr>
<tr>
<td>Lloyd et al. (2005)</td>
<td>1 14</td>
<td>T2N1M0 left</td>
<td></td>
<td>Neck dissection, hemiglossectomy, mandibulotomy and free flap reconstruction</td>
<td>Delivery at 40 wk a HB</td>
<td>Postoperative RT</td>
<td>0.3</td>
<td>NA</td>
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<tr>
<td>Prado et al. (2008)</td>
<td>1 16</td>
<td>T2N2M0 left</td>
<td></td>
<td>Neck dissection, tumor excision Postoperative RT</td>
<td>Delivery at 36 wk a HB</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lasar et al. (1995)</td>
<td>1 25</td>
<td>T2N1M0 left</td>
<td></td>
<td>Wild excision 8 wk after: neck dissection</td>
<td>Delivery at 36 wk a HB</td>
<td>RT</td>
<td>2.5</td>
<td>NED</td>
</tr>
<tr>
<td>Shibuya et al. (1987)</td>
<td>1 28</td>
<td>T2N0M0 right</td>
<td></td>
<td>RT</td>
<td>Caesarean at 34 wk a HB</td>
<td>Brachytherapy, neck dissection and Postoperative CT 4 months after delivery for recurrence</td>
<td>4</td>
<td>NED</td>
</tr>
</tbody>
</table>

Abbreviations: Wks: weeks, yr: years, HB: baby, RT: radiotherapy, CT: chemotherapy, NED: no evidence disease, NA: not available.
of the oropharynx associated with a reduced size of the glottis opening may lead to difficult intubation and ventilation, making loss of airway control one of the most common causes of death during anesthesia in pregnant women (Ni Mhraitíocháin and O’Gorman, 2006; Hawkins, 2005). Lowered systemic peripheral vascular resistance and compression of the inferior vena cava due to the enlarging of the uterus associated with circulation changes related to anesthetic agents and surgical manipulation may induce severe hypotension (Restman and Flood, 2011). This, together with maternal hypoxia or extreme hypercarbia or hypcarbia may be responsible for intrauterine fetal asphyxia (Van De Velde and De Buck, 2007). Even though surgery during pregnancy seems to be associated with increased fetal loss, pre-term labor and pre-term delivery (Ni Mhraitíocháin and O’Gorman, 2006; Restman and Flood, 2011), prophylactic tocolytic therapy has not been proven to be effective (Neplova and Johnson, 2012). Ideally, the second trimester is the safest period in which to perform surgery as the risk of premature labor is reduced (Van De Velde and De Buck, 2007). At the BEO, a comprehensive cancer center without obstetric- or neonatal intensive care unit facilities, after the 25th week of gestation the patient is referred for surgery where fetal monitoring and neonatal and obstetric assistance is available. Anesthesia is safe during pregnancy but should be judiciously planned and performed in a safe environment for both the mother and the fetus.

3.3. The Radiation Oncologist’s point of view

Radiotherapy during pregnancy is usually contraindicated due to the potential damage to the developing fetus. The radiation exposure to the fetus arises from: (1) radiation leakage through the linear accelerator (2) radiation scattered from the collimators and beam modifiers and (3) radiation scattered within the patient during the treatment. The most important technical factors are: the field size, the distance of the fetus from the field edge and the energy used (for the possibility of neutron production with energy greater than 10 MeV). Of equal importance to the technical aspect is the gestational age: during the first ten days of embryo development, the most frequent effect of radiation exposure is embryo death. From the 2nd to the 6th week of gestation (organogenesis phase), radiation exposure may be associated with fetal malformations and growth retardation. During the 12th until the 16th week (fetal period) of gestation, fetal exposure to ionizing radiation may be associated with permanent growth retardation and mental retardation. From the 20th week of gestation, sterility, malignancies, and genetic defects are the most frequently reported side effects of radiotherapy (Pavlidis, 2002; Bhalvat et al., 2009; Amant et al., 2010b; Martin, 2011). The threshold for all the above-described unwanted effects is considered 100 mGy. A fetal dose between 50 and 100 mGy is possibly associated with fetal alterations, while a dose below 50 mGy is probably safe (Stovall et al., 1995). Despite there being reports of a few cases of pregnant patients with oral cavity tumor safely treated with radiotherapy (Mhaleem Gziri et al., 2013) the literature data, in this setting of patients, are not yet conclusive. For this reason, we suggest that alternative treatments to radiotherapy during pregnancy be evaluated. If pathological findings suggest that postoperative radiation is needed in high-risk patients early delivery may be considered according to gestational age and patient’s wishes.

3.4. The Medical Oncologist’s point of view

The indications for chemotherapy in patients affected by oral tongue cancer are to be considered within the contexts of: adjuvant therapy, the curative setting and in patients with advanced stage of disease. In the adjuvant setting, chemotherapy is not recommended as monotherapy. It is always recommended in combination with radiation for patients with a postoperative high risk of recurrence: positive margins of resection and/or extranodal extension of disease (Kersten et al., 2004). The recommended treatment for these patients is high-dose cisplatin (100 mg/m2) administered every three weeks for a total of 3 cycles (Granata et al., 2009).

A weekly regime of administration has also been reported but there are no supporting phase III studies in this regard (Goerg et al., 2014).

As reported, patients #4 and #6 received postoperative treatment after delivery and surgery: it was the recommended treatment and it might be administered without any further strategy customization.

In the curative setting, chemotherapy is administered concomitantly with radiation as an alternative to surgery but it is generally considered a secondary option for oral tongue cancer.

The risk related to radiation in pregnant women, for both mother and fetus, has already been discussed. Chemotherapy may increase this toxicity and it is therefore contraindicated (Boeckman et al., 2005; Myott et al., 2002).

Chemotherapy could be the only feasible option for pregnant women with an unresectable tumor. To the best of our knowledge there are no studies regarding chemotherapy in pregnant women affected by head and neck cancer (Pignon et al., 2000; Posner et al., 2007; Vermorken et al., 2007; Lorch et al., 2011; Posner et al., 2009).

Regarding metastatic disease, platinum-based chemotherapy (either cisplatin or carboplatin plus fluorouracil) and cetuximab are the first-choice treatments. In particular, cetuximab has been demonstrated to improve survival in patients with recurrent-metastatic head and neck cancer (Vermorken et al., 2008). In pregnant women, the treatment should be started after delivery when possible. In this way the mother could receive the optimal treatment with the best chance of disease control.

Chemotherapy in pregnant women has been reported in hemato logical malignancies and in breast cancer, after the first trimester. Chemotherapy is teratogenic when administered by the 14th week of gestation (Cardnick and Iacobucci, 2004). There are few published studies reporting the use of cisplatin in pregnant patients (Amanat et al., 2009; Marnez et al., 2010). While the short-term outcome of newborns seems to be reassuring, there are no long-term data regarding the effects of cisplatin in prenatally-exposed babies.

Significant blood concentrations of cisplatin have been detected in the cord of two newborns exposed during the third trimester. Hearing impairment and ventriculomegaly have been reported in other cases after maternal treatment with cisplatin, even though the correlation is uncertain (Elli et al., 1998; Arango et al., 1994; Rafties et al., 1989).

5-Fluorouracil has been used during pregnancy in association with antracyclines and cyclophosphamide in breast cancer (Cardnick and Iacobucci, 2004). Nonetheless, the dosage and the schedule used for the treatment of head and neck cancer are different from those used in breast cancer. Thus, the standard combination of high-dose cisplatin and prolonged infusion of 5-fluorouracil cannot be recommended during pregnancy. As an alternative, the combination of carboplatin and paclitaxel were shown to be active in squamous cell carcinoma of the tongue in young adults (Kok et al., 2012) and have been used for the treatment of ovarian and lung cancer during pregnancy (Mancari et al., 2014; Azim et al., 2009). In the rare case of metastatic or unresectable tongue carcinoma, this combination may be used after the first trimester as palliative treatment.
3.5. The Neonatologist’s point of view

Due to the relative rarity of pregnancy-associated cancer, large prospective studies on this topic are lacking, and decisions about treatment should be made individually for each patient. Special attention must be placed on timing of delivery, since a preterm birth can affect neonatal outcome.

It is known that preterm birth, defined as childbirth occurring at less than 37 completed weeks of gestational age, is the leading cause of perinatal mortality and morbidity in developed countries, and has long-term adverse consequences for health (Saigal and Doyle, 2008). About 75% of perinatal deaths occur in infants born prematurely, with over two thirds of these arising in the 30–40% of preterm infants who are delivered before 32 weeks’ gestation (extreme–severe prematurity) (Goldenberg et al., 2008). Even though survival rates have greatly improved in recent decades for preterm infants, primarily as a result of advances in neonatal care, these infants remain at risk of developing a wide array of short and long-term complications, such as respiratory distress syndrome and intraventricular haemorrhage in the neonatal period, and bronchopulmonary dysplasia and neurodevelopmental impairment in early childhood (Saigal and Doyle, 2008).

However, mortality and morbidity are strongly inversely related to gestational age, and this should be considered in planning the childbirth. In extremely preterm infants (<28 weeks’ gestation), mortality rate ranges approximately from 10% at 27 weeks to more than 60% at 23 weeks, decreasing to 3–7% in severe preterm infants (28–31 weeks), while a survival rate of almost 100% can now be expected in infants delivered at or after 32 weeks’ gestation in developed countries (32–33 weeks = moderate prematurity; 34–36 weeks = near term or late-preterm). Morbidity and long-term sequelae are also inversely related to gestational age, with the highest rates of neurodevelopmental impairment, respiratory diseases and gastrointestinal complications in infants delivered before 32 weeks’ gestation (Stoll et al., 2010). However, no gestational age is wholly exempt from disease. In recent years, a broad range of neonatal complications has been documented in the growing body of literature on late-preterm infants. These problems include delayed lung fluid clearance (transient tachypnea of the newborn), respiratory distress syndrome, pulmonary hypertension, apnea, temperature instability, hypoglycemia, jaundice, and pooping. A higher rate of re-hospitalization and difficulties in motor skills, speaking, writing, and behavior has also been reported (Saigal and Doyle, 2008). These data should be considered when delivery at these gestations is planned. Certainly, the pregnant patient and her family should be thoroughly informed about the illness and the therapeutic options, and the final decision should be made together with the patient, after careful consideration of both the risks and benefits.

3.6. The Obstetrician-Gynecologist’s point of view

Evaluation and care of pregnant women with cancer should be performed in a maternity center with appropriate assessment and care of infants at high risk, with the possibility of following intrauterine fetal growth and checking the preterm contractions of the uterus, particularly after the 25th gestational week. The characteristics of the amniotic fluid and placenta should also be tested (Van Calsteren et al., 2010). In the same unit, a neonatology and pediatric service should be present to address any fetal problems and provide consultation for the parents.

At the diagnosis of tongue cancer, progressing pregnancy should be confirmed and the duration defined. The possibility of any pre-existing fetal anomalies should be excluded by ultrasound. Maternal care before and during the peripartum period is the best insurance for fetal wellbeing. During the second or third trimester of pregnancy the use of fetal heart-rate monitoring during surgery is mandatory to detect fetal distress and the activity of the uterus. Sometime preterm onset of labor can be provoked by pain, thus sufficient analgesia is needed. Postoperative tocometry will identify any uterine activity that is masked by analgesia (Werkoff et al., 2008; Amant et al., 2014).

According to the opinion of The American Congress of Obstetricians and Gynecologists (ACOG Committee), if the fetus is considered pre-viable, it is sufficient to ascertain the fetal heart rate before and after the surgical procedure. If the fetus is considered to be viable, simultaneous electronic fetal heart rate and contraction monitoring should be performed before, during and after the surgery (Nonobstetric Surgery During Pregnancy, Committee opinion, 2011). Moreover, since pregnancy is an added risk factor for thrombosis, apart from the malignant disease, thromboembolism with low-molecular-weight heparin is indicated. This strategy is also indicated during puerperal admission. From an obstetric point of view, the ideal time for delivery is at least the 34th week. Breastfeeding in the absence of maternal emergencies is recommended (Amant et al., 2014; Nonobstetric Surgery During Pregnancy, Committee opinion, 2011).

In this paper no interruption of pregnancy was indicated in instances of poor maternal prognosis or urgent need for cancer treatment in the first trimester. The findings of this study show an overall good outcome of those pregnancies complicated with tongue cancer.

3.7. General considerations

When treating tongue cancer during pregnancy some factors should be considered: the gestational age at diagnosis, the prognosis of the specific malignancy (e.g. histologic type, site, stage), and the patient’s wishes regarding pregnancy.

In our cases, we favored surgery over radiation to reduce the possible impact of radiotherapy on the fetus, to decrease the possibility of jaw radionecrosis and to avoid the risk of second primary tumor in the irradiation area, which is especially high in young patients (Strong, 1990; Layton et al., 1992; Lawson and Breslow, 1996).

Tongue carcinoma is known to be strongly related to the presence of micrometastases and skip metastases. Homolateral neck dissection should be performed 4 weeks after tongue surgery in patients whose pathologic specimen shows a tumor thickness greater than 3 mm (Shah and Gil, 2009; Spiro et al., 1986; Pimenta et al., 2004).

Three of the six cases presented (cases #1, #2 and #3) had a small cT1 tumor treated with a wide excision; all of them had good outcome without any oncological, fetal and maternal problems.

For the last three patients (cases #4, #5 and #6) a personalizedized treatment was proposed, for fear of damaging the fetus with prolonged surgery or chemoradiation. Unfortunately, this approach possibly impaired maternal prognosis based on currently available guidelines. Two of these patients (patients #4 and #6) should have received neck dissection at no more than 4 weeks from initial surgery (tumor thickness > 3 mm), while patient #5 should have received major surgery followed by radiotherapy at no longer than 3 months after surgery. Even though guidelines for pregnant patients are not available, according to the literature, applying standard treatment to high-risk patients may probably decrease local and distant metastases and improve maternal survival (Mihalem Gazi et al., 2013), Table 2. Nonetheless, other factors that drove treatment choice in these the patients should be taken into consideration. Physicians who treat pregnant mothers with tongue cancer are often overwhelmed with decisions that include the mother, the fetus and their personal beliefs. So far the issue seems to be one of choosing between maternal advantage and potential fetal damage.
Looking at this issue within the framework of a multidisciplinary approach and an exhaustive literature review (Table 2), surgery during pregnancy today seems to be a safe procedure in keeping with a normal course of pregnancy, if well-planned in a prepared hospital care center. Elective termination of pregnancy is a possibility that should not be considered, and the mother and others family members involved should be reassured by this: treating the oral cancer employing the surgical standard procedure while at the same time safeguarding the baby’s health is now possible. The surgical oncologic treatment can be optimally managed together with the obstetrical aspects in a specialized maternity center.

From this perspective, in oncological diseases where surgery is the first choice treatment, as is the case with tongue cancer, following the standard surgical procedure seems to be the correct approach, entailing lower risk for the fetus and best outcome for the mother.

Nonetheless, choosing between maternal advantage and potential fetal damage should not be an individual decision. Patients and their families should be provided with comprehensive and appropriate information and support in order to participate in the decision-making process. Doctors should discuss all rare cases such as these within a multidisciplinary meeting and share with their patients the uncertainties and drawbacks of the different scenarios that may be suitable for each individual situation. When “customization” occurs, it should be clearly stated on what basis the decision was made and involve the contribution of health care providers, patients and their family members (Yokoshima et al., 2012; Atabo and Patrick, 2008; Koike et al., 2005).

4. Conclusions
When tongue cancer is diagnosed in a pregnant woman, both the clinician and the patient see faced with difficult decisions. From the experience gained with our series of patients, and from a review of the literature, we are inclined to suggest that pregnant patients with tongue cancer should follow standard oncological treatments. Today, surgery during pregnancy seems to be a procedure which is both safe and compliant with a normal course of pregnancy. A multidisciplinary discussion of each individual case should be pursued to improve maternal and fetal outcome, but surgery seems to be the most correct and the safest way to ensure both. The idea of economizing on surgical treatment for fear of damaging the fetus does not seem to be supported by clinical practice and in the end only serves to bring about the opposite goal. Nonetheless, it must always be borne in mind that an oncological treatment can by no means be considered correct unless it meets with the wishes of the patient and her family.

Conflict of interest
None of the authors have any conflict of interest.

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