Adenoid Cystic Carcinoma of Head and Neck

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Abstract

Adenoid cystic carcinoma is an uncommon salivary gland tumour that often may arise with an advanced stage at diagnosis. The clinical and pathological patterns are characterized by slow growth, peri-neural invasion, multiple local recurrences and distant metastases. The optimal treatment is generally radical surgical resection and is almost always followed by postoperative radiotherapy. Much effort has been invested in understanding the tumour’s molecular biological processes, aiming to identify patients at high risk of recurrence, in hope that they could benefit from other, still unproven treatment modalities such as chemotherapy or biological therapy. This article provides an update on the current understanding of adenoid cystic carcinoma of the head and neck, including a review of its epidemiology, clinical behavior, pathology, molecular biology, diagnostic workup, treatment and prognosis.

Keywords: Adenoid cystic carcinoma; Head and neck; Salivary glands; Review

Introduction

In 1853 Robin, Lorain and Laboulbene first described two cases of an uncommon epithelial tumour of the nose and the parotid gland [1], which was named “cylindroma” by Billroth in 1856 [2]. Only in 1930 Spies introduced the term “adenoid cystic carcinoma” (AdCC), and until 1940’s AdCC was considered a benign variant of the mixed salivary gland tumour [3]. The malignant nature of this neoplasm was finally explained by Dockerty and Mayo in 1943 [4].

AdCC represents about 10% of salivary gland tumours [5] and about 1% of all head and neck malignant neoplasms [6]. Although AdCC is rare, it can be considered the most common malignant neoplasm of the submandibular and minor salivary glands [6,7] but it can also occur in different sites of head and neck regions where secretory glands are, such as nose and paranasal sinuses, trachea, larynx and even lacrimal and ceruminous glands [7-10].

AdCC frequently appears as a small, slow growing, lesion, but it is often discovered at an advanced stage [11]. The main characteristics of this type of neoplasm are peri-neural invasion, which occurs in around 22% to 46% of cases, and multiple local recurrences [12]. Regional lymph-node involvement is considered rare [1,2]. However, distant metastases have a 40% incidence [13], with lung, bone, and liver representing the most commonly affected sites [3]. Clinically, pain is the main symptom [14]. The treatment of choice is represented by radical surgical resection, often followed by post-operative radiation therapy and, in selected cases, by chemotherapy [7,14]. Minor salivary gland AdCCs seem to have a worse prognosis than the major salivary glands’ ones. In most cases, this neoplasm has a long course and uncertain prognosis. It has been observed that some asymptomatic patients affected by advanced and unresectable AdCCs who were not treated, as well as patients with stable metastatic disease, may survive even for 10 years to 15 years [15].

Epidemiology: Adenoid cystic carcinoma represents 10% to 12% of all salivary gland tumours and 3% to 5% of head and neck carcinomas [7]. AdCC has a global incidence of 3 to 4.5 cases per million per year, declining from 1993 to 2007, especially for early stages [7,16]. The 5th and 6th decades are commonly involved, with higher frequency in middle-aged and older patients [7,17]. Many studies proved that AdCC is more frequent in the female population (2:3 M:F) [18-20].

In the head and neck district, the majority of AdCCs arises from minor salivary glands (75%), representing about 1% to 2% of tumours (25% of malignant neoplasms); the main affected sites are palate and paranasal sinuses (14% to 17%) [2,3,21,22]. Ko et al. [22] stated that the tumour location in minor salivary glands was associated with a higher risk of recurrences and with a worse prognosis. 40% of salivary gland AdCCs occurs in the submandibular gland [5]. Haematogenous metastases are common, whereas lymph-node involvement is so rare that in patients with cN0 neck dissection is generally not necessary [21]. There are no assessed risk factors for AdCC [23].
Histopathological features: Dardick hypothesized that AdCC, currently defined as a basaloid tumour, arises from specific sections of ductal-lobular unit, a theory that was recently confirmed [24,25]. Microscopically, AdCC is composed of small basaloid epithelial, non-luminal, hematoxyphilic cells, with small or moderate cytoplasm. Generally, nuclei are not so pleomorphic, with small or bland nucleoli. This type of tumour shows a predominant myoepithelial differentiation [3].

Three distinct architectural patterns- tubular, cribriform and solid have been derived, derived by the combination of basal myoepithelial cells and luminal epithelial cells; generally, AdCCs show a variable mixture of two or three of these patterns, with the prevailing architectural pattern determining the category. Cribriform pattern is the most frequent and is composed of basaloid cells organized in oval-rounded masses of variable size, punched-out by rigid, oval, cyst-like spaces (pseudolumina) that may contain “cylinders” (i.e. globules of hyaline material and/or myxoid glycosaminoglycans) and, occasionally, small “true lumina” lined by luminal cells, composing a “swiss cheese”-named model (Figure 1A). Tubular pattern is characterized by tubules lined of luminal cells enclosed by non-luminal cells with, usually, clear cytoplasm (Figure 1B). Solid pattern is composed of basaloid cells growing in sheets without lumina formation [24,26]. Commonly, AdCC is composed of cribriform and tubular patterns (Figure 1C) [27]. All variants can show a prominent perineural invasion, and the tumour can follow the course of a nerve for a long distance; the neoplasm can also show intraneural invasion, considered an independent negative prognostic factor [3,28].

Currently, there are two grading system for AdCC, with the cut-off value to predict a worse prognosis based on the amount of the solid component: >30% according to Perzin and Szanto, >50% for Spiro [29-31].

According to Szanto et al., the grades are:
- Grade I: tubular and cribriform pattern, without solid component;
- Grade II: pure cribriform pattern, or mixed with >30% of solid component;
- Grade III: predominantly solid pattern.

Low-grade tumours are more likely found in palate or in parotid gland, while high-grade ones are generally observed in submandibular glands [30]. Van Weert et al. [32] recently proposed a new grading system, based on the presence or absence of solid pattern, which is correlated to a worse prognosis (Table 1).

Immunohistochemical and molecular features:
Immunohistochemistry represents an essential tool in diagnosis of AdCCs that express a characteristic immunohistochemical pattern.

In 1988, Chen et al. [33] divided AdCC into two immunohistochemical groups: the first group had positivity for Carcinoembryonic Antigen (CEA), Epithelial Membrane Antigen (EMA), low and high molecular weight Cytokeratines (CK) and S-100 (Figure 2); the second one had the expression of Smooth Muscle Action (SMA) and low molecular weight CK [34]. Only in 2009 was found that the first group found by Chen corresponded to luminal cells, whereas the second one corresponded to myoepithelial cells, which were also positive for vimentin, p63, and S-100. Peri-neural invasion seems to be correlated to expression of S-100 and Glial Fibrillary Acidic Protein (GFAP), which indicates Schwann cell differentiation in modified myoepithelial cells. Other immunohistochemical features are also the expression of beta-catentin, E-cadherin and a high (90%) expression of c-KIT (CD117), p53, and a low Ki67; in particular, the majority of luminal cells expresses CD117, and so it can be considered an important diagnostic criterion [7,34,35]: expression of c-KIT is associated to high-grade and solid pattern, and may play a role in local invasion and development of distant metastases [36]. Recent studies have highlighted that CD43 (lymphoid antigen of T-cells) is expressed in cytoplasm and cytoplasmic membrane in 45% to 100% of AdCCs [37]. SOX-10, a transcription factor, is also considered an efficient immunohistochemical marker [38]. Other molecular markers are represented by VEGF, usually over expressed in 85% of AdCCs, and EGFR (20%) [35]. Over-expression of EGFR is correlated to a better prognosis in AdCC [38]. According to Meis et al. [39], two variants of AdCC can be defined: a conventional low-grade and a high-grade de-differentiated carcinoma, the latter associated to higher proliferation rates, high values of Ki67, and loss of myoepithelial markers [40] (Figure 3). Immunohistochemical study is mandatory in order to identify solid and de-differentiated areas: Her-2/Neu amplification, as well as hyper-expression and Loss of Heterozygosis (LOH) of p53, is present widely and only in de-differentiated areas [41].

Zhao et al. [42] analysed the immunohistochemical expression of SKA1 and MMP-9, and found that it was associated with advanced stage and solid pattern; in particular, SKA1 was associated with local recurrence and peri-neural invasion, while MMP-9 with a worse TNM staging and lower survival rates.

In terms of genetics, the most important molecular event related to AdCC is a specific translocation: t(6;9)(q22-23; p23-24), which fuses the MYB oncogene (6q22-q23) to the transcription factor gene NFIB (9p23-p24), leading to the potential activation of MYB targets, such as apoptosis control, cell cycle control, and cell growth genes [43,44]. According to Hudson et al. [45], the translocation MYB-NFIB has a sensitivity of 50% and specificity of 100% in differentiating between AdCC and pleomorphic adenoma. MYB rearrangement seems to have an important prognostic role, particularly in the cribriform and solid variants, in predicting the risk of local recurrence and distant metastases [46]. Bell et al. [47] found a transcription factor EN1, related to histologic grade and poor prognosis, and silenced by hyper-methylation. Next generation sequencing techniques showed that, in addition to MYB-NFIB rearrangement observed in 80% to 90% of AdCC, other genetic alterations could be found: mutation of catalytic domain of PTEN, present in 30% of cases, seems to activate the way of PI3K, AKT and mTOR [38]; alteration of NOTCH way is related...
persistent and recurrent growth pattern; death is frequently caused by a long-term, indolent course, but it has an aggressive, unpredictable behavior with malignancies. It seems to have a predilection for the head and neck region, and bone involvement can be possible. Palatal and maxillary sinus tumors are characterized by mucosal ulceration and, if the tumor arises in the palate, can spread through the greater and lesser palatine foramina. Primary AdCC most frequently occurs in the pterygopalatine fossa, the greater and lesser palatine canals and the foramen rotundum, vidian canal, infratemporal fossa through the orbital apex, inferior orbital fissure, cavernous sinus, and as a pathway of tumor extension due to its anatomical connection with the cranial nerves, decreases to 63%.

Preclinical evidences suggest an important role of FGF1, FGF2, and FGFR1 over-expression in AdCC carcinogenesis. Clinical patterns: On macroscopic examination, AdCC usually presents as an asymmetrical, slow-growing, unilobular, hardened lesion, with or without a partial capsule, often showing an invasive growth pattern into adjacent tissues. According to the site of onset, symptoms are different: in major salivary glands, the tumor produces mass effect, while in the parotid gland, facial nerve paralysis may occur; dyspnea may occur in tumors affecting the larynx; nasal obstruction, deep facial pain, epistaxis and eye-related symptoms are common in nose and paranasal sinuses AdCCs. Perez et al. [50] described 129 cases of AdCC characterized by the presence of a hardened lump (92.1%), pain (59.8%), paresthesia (12.6%) and nasal congestion (11.8%). Pain is a common and important finding in AdCCs with peri-neural invasion [3,20]: the maxillary (V2) and mandibular (V3) branches of trigeminal and facial (VII) nerve are most frequently involved in peri-neural spread, and represent a way to tumour infiltration into the pterygopalatine fossa (PPF), Meckel’s cave and cavernous sinus [51]; in particular, PPF is a major pathway of tumour extension due to its anatomical connection with the orbital apex, inferior orbital fissure, cavernous sinus via the foramen rotundum, vidian canal, infratemporal fossa through the pterygomaxillary fissure, the greater and lesser palatine canals and the sphenopalatine foramen [52]. Primary AdCC most frequently occurs in the palate and can spread through the greater and lesser palatine nerves into the PPF [51,52], while the facial nerve is involved in parotid AdCC and, through the stylomastoid foramen, the neoplasm can spread into the petrous apex [51]. The connections between the trigeminal and facial nerve through the vidian nerve, Greater Superficial Petrosal Nerve (GSPN) and auricolotemporal nerve have to be considered; in particular, after leaving the geniculate ganglion of the facial nerve, the GSPN runs anteriorly into foramen lacerum, joins the deep petrosal nerve and enters the vidian canal as vidian nerve [53]. The auricolotemporal nerve is formed by two roots arising from V3, which encircle the middle meningeal artery and enter the parotid gland to join the facial nerve [51,54]. Intraoral AdCC localization is characterized by mucosal ulceration and, if the tumor arises in the palate or maxillary sinus, bone involvement can be possible [55].

AdCC has been defined as one of the most biologically destructive and unpredictable tumors of the head and neck [50]: it seems to have an indolent course, but it has an aggressive, long-term behavior with persistent and recurrent growth pattern; death is frequently caused by metastatic spreading of the disease [17]. Distant metastases are generally observed in 25% to 55% of patients and involve the lung in up to 40% of cases; liver, kidney, bones, and brain can also be affected [1,2]. Lymph-node metastatic localizations are rare, seen only in 5% to 25% of cases and are not yet a reliable prognostic marker [56].

**Diagnosis:** Preoperative imaging is mandatory in the diagnosis and staging of AdCC. Ultrasound examination is generally used for initial detection of AdCC, but there are no specific features to distinguish AdCC from other neck neoplasms: irregular margins and a disomogenous hypochogenic structure, often with cystic pattern, being common features of most malignancies [57,58]. Ultrasound-guided fine needle aspiration cytology can help distinguish malignant and benign lesions: the accuracy of this procedure is dependent by the operator’s experience, with a sensitivity of 88% to 93% and a specificity of 75% to 99% [59].

The most important feature diagnostic imaging has to evaluate is the anatomical extension of the disease, which is crucial for an accurate surgical planning; obviously, CT can better delineate bone invasion, while MRI is preferred for the evaluation of the lesion nature, the assessment of loco-regional extension across deep planes, and cervical lymph-nodes and bone marrow infiltration [60]. The study of the skull base is mandatory to investigate intra-cranic localization of disease through retrograde peri-neural pathway, and as important as its caudal extension to the cervical-thoracic passage. MRI study technique includes conventional morphologic T1 weighted and T2 weighted sequences, as well as Diffusion Weighted Imaging (DWI) sequences. Primary AdCC can be seen both as a defined mass or an ill-defined mass with diffuse infiltration of the surrounding structures; generally, it homogeneously enhances after contrast-media injection, although heterogeneous enhancement due to necrosis can occur [60]. The solid and more cellular histological subtype of AdCC has lower signal on T2-weighted MRI imaging [61]. Irregular margins, adjacent tissue infiltration and hypointensity in T2-weighted sequences are characteristic of salivary gland carcinoma, respectively with decreasing predictive value [61]. Apparent Diffusion Coefficient (ADC) allows distinguishing between AdCC and pleomorphic adenoma, but has a low predictive value of malignancy [62]. Dynamic Perfusion-Weighted (PWI) sequences increase MRI sensitivity for carcinomas, but not specificity; AdCC often shows a rapid wash-in from plateau, which is also typical in pleomorphic adenoma, but with much lower ADC values [63]. A recent study by Singh et al. [58] described all the imaging features of peri-neural tumour spread: enlargement/erosion of foramen, nerve enlargement/enhancement, obliteration of the peri-neural fat tissue layer, including PPF, enlargement and convexity of the lateral cavernous sinus wall, soft-tissue replacement of cerebrospinal fluid-filled Meckel’s cave, muscular denervation; in particular, muscular denervation can be considered a secondary sign of nerve damage: firstly, in acute and sub acute stages, oedema appears, while the chronic appearance is characterized by fatty replacement of muscle tissue and by muscular atrophy [64]. However the possibility that many other conditions, such as infection, inflammation, trauma, vascular lesion, and haematomata can mimic a neoplasm of the head and neck region must be considered [57]. MRI is superior to CT in sensitivity (95% to 100%) in detecting AdCC’s peri-neural spread along the skull base, but the sensitivity, when mapping the extent of disease, decreases to 63% [65]. CT is complementary to MRI in the study of local bone changes and of the skull-base foramina [57].
Moreover, MRI represents the gold standard for post-therapy follow-up, while whole-body CT and 18F-FDG PET-CT can be used to detect distant metastases, particularly in initial staging and in post-treatment monitoring [65,66].

Treatment: Radical surgery with wide resection margins represents the treatment of choice in AdCC [3]; however, the goal of obtaining disease-free margins is generally not achieved due to both AdCC’s frequent tendency to peri-neural invasion and the challenging anatomical access some lesions can present with. In this regards, Casler et al. [67] highlighted that, despite a pre-operative planning of a complete excision, 80% of skull-base AdCCs had positive surgical margins at the extemporary histological examination.

A superficial or total parotidectomy is required in all cases of localized or diffuse/deep parotid gland AdCC, respectively. Generally, facial nerve is preserved through intra-operative monitoring, in order to minimize injury; if a clinical or microscopic evidence of tumour infiltration of the facial nerve is present, it should be appropriate to sacrifice its main trunk or the involved branches. The surgical margins of both the distal and proximal nerve stumps need to be free from disease, due to the strong tendency of AdCC to peri-neural invasion. Should the tumour extend beyond the parotid gland, a resection of surrounding skin or masseter muscle, mastoidectomy, temporal bone resection, mandibulotomy or an excision of the contents of the infratemporal fossa may be suggested [33]. In case of a localized tumour of the submandibular gland and for every tumour involving the structures of the submandibular triangle (hypoglossal or lingual nerves, digastric or mylohyoid muscles, floor of mouth or mandible), an “en bloc” resection is required; particular attention should be made to possible peri-neural invasion [34].

The surgical treatment of minor salivary glands AdCC depends on the site of origin and on the extent of the tumour: a local resection in case of localized AdCC of the oral cavity may be appropriate, or, if the AdCC is extended, a radical excision is necessary, including marginal or segmental mandibulotomy, and/or partial or total resection of the hard or soft palate [34].

AdCC of paranasal sinuses should be treated with partial or total maxillectomy, infratemporal fossa dissection, and/or anterior craniofacial resection; in these cases, peri-neural invasion may involve the branches of the second and third division of the trigeminal nerve [34].

Lymph-node metastases are only occasionally seen in AdCC [3]; however, a significant incidence of cervical lymph-nodes metastases in almost 10% of AdCCs of the tongue and mouth floor has been described [68]. It also has been reported a 15.4% of occult metastases in elective neck dissection cases. On this basis, elective neck dissection is recommended by some Authors for staging and achieving regional control of the disease [62]. Nonetheless, it is still difficult to understand whether regional control is improved by an elective neck dissection rather than neo-adjuvant radiation therapy on neck lymph-nodes [13].

The role of adjuvant therapy is still controversial; in particular, a combined treatment with Radiation Therapy (RT) and surgery is preferable; Shah et al. [69,70] demonstrated excellent results in local disease control in patients treated with surgery and post-operative RT. Important results were obtained in patients with submandibular gland and minor salivary gland AdCCs [34]. Chen et al. [71] analysed 140 cases of AdCCs, comparing prognostic features of recurrence between patients treated with surgery with or without RT, confirming an improvement in local disease control in patients treated with adjuvant RT. Furthermore, many studies show that post-operative RT does not affect the course of the disease; however, it is commonly performed in patients with regression and/or relief of symptoms, as well as in cases of skull base disease, with peri-neural invasion, neck lymph-nodes metastases, recurrent tumours and solid histological subtype [71,72]. Katz et al. [73] showed that post-operative RT seems to delay, rather than prevent, local recurrence. According to Adelstein et al., [34] RT can be useful in achieving tumour reduction and, in all cases of unresectable tumours, as symptomatic palliation. In additional to traditional RT with photons, other techniques have been recently used: therapy with neutrons, C12 ions, protons, combined therapy with Intensity Modulation RT, and with a C12 ions boost [74]. Neutron RT is associated with higher rates of local disease control (75% at 5 years), whereas C12 ions RT demonstrated to control locally solid growth AdCC and improve OS and PFS [75].

Systemic chemotherapy represents another controversial treatment, due to low sensitivity of AdCCs to this kind of treatment; however, palliative chemotherapeutic treatment proved to be useful in a small percentage of patients with recurrent or metastatic disease. The choice of first-line chemotherapy needs to be based on patient’s characteristics and comorbidities [76]. In a recent systematic review by Laurie et al. [77,78], as well as in other clinical trials, polichemotherapy based on platinum is correlated to better results (25% of therapeutic response). A phase-II study on AdCC treated with taxol demonstrated a 3-year OS of 43%; in contrast, a trial with gemcitabine in 21 advanced AdCC reported no treatment response [79,80].

Recently, new target drugs have been evaluated: AdCC seems to respond to Imatinib mesylate; other useful agents are represented by Cetuximab, Gefitinib, Lapatinib, Lenvatinib, EGFR-inhibitors (Dovitinib) and anti-angiogenics (Sorafenib, Axitinib) [81-84]. Combination of RT and chemotherapy with various agents could represent a useful alternative: Schoenfeld used, in HER-2/Negative tumours, Trastuzumab in association with Carboplatin or Paclitaxel, the last ones acting as radiosensitzers [3,85]. Dasatinib has demonstrated tumour stabilization in 50% of progressive cKIT-Positive AdCC [86]. In case of chemotherapy failure, best supportive care treatment or experimental clinical trials could still represent a choice.

Prognosis: Many authors consider AdCC a “clinically high grade” neoplasm; however the prognosis is still difficult to assess, due to the different quality of reports and length of follow-up [3].
A better prognosis is linked to tubular and cribriform histological subtypes, rather than the trabecular and solid ones, which are correlated with higher recurrence, early distant metastases, and higher mortality rates [28,29]. The association with biomarkers like c-KIT, VEGFR-3, Ki-67 and p53 corresponds to a greater tumour malignancy [27,87].

Tumour localization seems to influence outcome: in head and neck district, major salivary glands tumours have a better prognosis than minor salivary gland ones. AdCCs originating in other sites such as breast or skin have a better prognosis than major salivary gland, lung, bronchi, and eye AdCCs [27,88]. Other important prognostic factors are cervical lymph-nodes metastases, advanced tumour stage, pathologic surgical resection margins, high histopathological grade, and macroscopic peri-neural invasion [89,90]. Recent data suggest that intra-neural invasion, rather than peri-neural invasion, has an important influence in outcome of patients affected by AdCC. Intra-neural invasion is defined as the presence of peri-neural invasion, with tumour cells in the nerve, and/or irregular destruction of axons; so, intra-neural invasion is considered an independent variable of worse prognosis, but it does not influence the development of distant metastases [55]. The presence of tumour-free surgical resection margins is a positive prognostic factor, due to a better local control and is associated with longer survival rates [88,89]; in addition, the extent of surgical margins had a significant impact on local disease control and on DFS rates, but not on OS rates, due to the indolent course of AdCC [88]. Eventually, other negative prognostic factors need to be considered. Among these, a tumour size greater than 3 cm, male gender and advanced age [13,29].

According to DeAngelis et al. [88] AdCC OS rates are 92%, 72% and 54% at 5, 10 and 20 years respectively, and patient survival rates decrease considerably in series with a follow-up lasting more than 15 years; on the other side, in a recent study by Van Weert et al. [21]. On 105 patients, survival rates were of 68%, 52% and 28% at 5, 10 and 20 years respectively.

There is a relationship between life expectancy and metastatic disease occurrence, with an OS at 5 years of 48% in patients with lymph-nodes metastases, and of 77% in metastases-free patients [91]. The average time between detection of lung metastases and death was about 32 months and between the occurrence of other metastases and exitus there were about 20 months; the explanation of these data may lie in the fact that extra lung metastases are discovered later, at a stage interfering with vital functions; it also seems that the AdCC’s lung metastases’ doubling time has an average of 32 months, suggesting that the tumour spreading at cellular level could occur before clinical presentation of primary neoplasm [92,93].

The site of metastatic disease seems to influence outcomes in patients affected by AdCC: lung metastases are associated to a better PFS and OS, while liver metastases increase the risk of death [94].

**Conclusion**

AdCC is a rare tumour, associated with low survival rates. It can be considered the most common malignant neoplasm of the submandibular and minor salivary glands. It has an indolent course and aggressive long term behavior, with persistent and recurrent disease. The main characteristic is represented by intra- and peri-neural invasion, which influence radical surgical management. Surgery represents the gold standard treatment in association with post-operative RT and chemotherapy. Development of distant metastases impairs treatment outcomes. Recent trials are looking for therapeutic alternatives to treat advanced AdCCs.

**References**

R De Berardinis, et al., American Journal of Otolaryngology and Head and Neck Surgery


R De Berardinis, et al.,
American Journal of Otolaryngology and Head and Neck Surgery


71. Münter M, Unnathum V, Nikoghosian A, Jensen AD, Hof H, Jaekel O, et al. Combination of intensity modulated radiation therapy (IMRT) and a carbon ion boost for subtotal resected or inoperable adenoid cystic carcinomas (ACC’s) of the head and neck. InPTCG meeting. 2009.


93. Li N, Xu L, Zhao H, El-Naggar AK, Sturgis EM. A comparison of the demographics, clinical features and survival of patients with adenoid cystic carcinoma of major and minor salivary glands versus less common sites within the surveillance, epidemiology and end results registry. Cancer. 2012;118(16):3945-53.