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VANDALIZING EFFECTS OF ORAL CANCER THERAPEUTIC PROCEDURES

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ABSTRACT

The occurrence of new cases of malignant tumors of the upper airways and digestive passages diagnosed in the world per year are about 870,000. In contrast to higher incidence rates of these malignancies in a developing countries, only neck cancer rates are been found to be highest and the choice treatment for these malignancies is surgery, associated or not with radiotherapy. Surgery and radiotherapy are the treatment options for the localized or regional disease. Since radiotherapy-induced oral complications cause high morbidity and a decrease in quality of life, the aim of this review is to acknowledge the main mutilating oral effects caused by oral cancer therapies and a special attention to be given to the post therapies adverse effects before initialization of any treatment.

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INTRODUCTION

With increasing dental awareness amongst the population, it is reasonable to expect that more and more dentate patients will be diagnosed with head and neck cancer. Many patients with head and neck cancer are submitted to high doses of radiotherapy in large areas including oral cavity, maxilla, mandible and salivary glands.¹ Despite having the advantage of preserving the tissue structure, radiotherapy causes many adverse reactions in the oral cavity. In dealing with patients with cancer of the head and neck a team approach is required for effective management. When radiation therapy is indicated, it is imperative that health of the oral cavity be assessed initially as well as throughout therapy. All members of the cancer treatment team should be informed of the oncologic treatment plan. Oral care should be initiated at the onset of treatment, with the goal of reducing morbidity and improving compliance.²

Effects of Radiation Therapy

Mucositis

Oral Mucositis is one of the first symptoms of radiation complications which occurs 10-15 days after the initiation of therapy. Oral mucositis can present as patchy mild erythema to frank confluent ulceration and the mucosal inflammation varies with dosage, target size and duration of therapy. Chemotherapeutic agents such as 5FU, procarbazine, methotrexate, etc., may increase the severity of these symptoms. Cultures may be needed to differentiate between fungal, bacterial and viral lesions versus those secondary to radiation effects. At present there are no drugs available to prevent mucositis, and it is imperative to distinguish these lesions from those caused by infections.

Prevention, on the part of the Radiation Oncologist is essential to minimizing excessive morbidity of the oral mucosa. This is accomplished by designing portals that limit the exposure to tissues not at risk for tumour recurrence. When interstitial

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implants are a part of a treatment protocol, soft tissues of the oropharynx are at greater risk for developing soft tissue ulcerations. Mucosa thickness, another important predictor of exaggerated tissue response, should be considered. The anterior commissures of the mouth and the medial surface of the angle of the mandible are sites which contain very thin mucosa and would benefit from field blocks if possible.²

Lack of saliva and damaged taste buds may alter the sensation of taste during radiotherapy. Often, patients complain that many foods taste excessively salty which may reduce the motivation for adequate oral intake. In response to their altered taste sensation, patients tend to compensate by increasing their intake of sugar. Counselling should be provided to avoid this behaviour due to the increased risk of dental caries. However, altered taste sensation is a transient phenomenon since the taste buds recover in two to four months post therapy.

Xerostomia

Radiation therapy may irreversibly affect the production and quality of saliva in the salivary glands. Doses as low as 20 Gy results in clinically noticeable changes leading to sparse thick ropy saliva. In particular, if the parotid glands are in a field which received 40Gy or over, permanent dysfunction of the salivary glands should be expected and discussed with the patient prior to treatment. Concomitant administration of medications which are known to induce xerostomia (i.e. psychotropics, antiemetics, antihistamines, and thousands of other commonly prescribed medications.) should be carefully considered.³

The diagnosis of xerostomia is based on subjective impressions by the patient and the clinician. Dry mouth may affect speech, taste, nutrition and the patient's ability to wear prosthesis. Saliva also contains antimicrobial compounds (i.e. sIgA, and mucins) which reduce pathogenic bacteria and decrease the risk of infection in the oropharynx. However, saliva's most important role lies in its ability to mechanically cleanse the teeth and soft tissues. Therefore, with radiation induced xerostomia it is common for this to lead to an increased incidence of caries, especially in the cervical portion of the clinical crown at the cemento-enamel junction. Henceforth, the change in salivary content and quantity also leads to an increased incidence of candidiasis and periodontal disease.⁴

Candidiasis

The symptomatic effects of radiation on the mucosa is intensified by colonization of yeast in oral candidiasis. The clinician should be able to identify and diagnose the varied presentation of candida including pseudomembranous (removable white plaques with an erythematous base), chronic hyperplastic (leukoplakia like plaques that do not wipe away), and chronic cheilitis.⁵ These infections should be eliminated to decrease mucositis and the chance of occurrence of gastrointestinal infections.

Bacterial Infections

The oral cavity may be the portal of entry for many systemic infections. Bacterial infections can lead to sialadenitis, periodontitis, abscesses, pericoronitis, or other causes of ulceration. Empiric treatment with antibiotics are usually adequate; however, periodontal lesions usually need additional

debridement. Therefore, chlorhexidine rinses should be considered for these patients. Gingival bleeding may be the first sign of thrombocytopenia. The patients' ability to accomplish adequate oral hygiene may be limited. In these instances flossing may have to be discontinued. Again chlorhexidine rinses may be required to reduce pathogens found in plaque.⁴

Chronic effects of Radiation Therapy

Osteoradionecrosis

Osteoradionecrosis (ORN) is a bone ischemic necrosis caused by radiation. Being one of the most serious consequences of radiotherapy, causing pain as well as possible substantial loss of bone structure⁵. Long term effects of radiation therapy on osseous and soft tissues are soft tissue fibrosis and ischemia, which may never resolve. The main mechanism of osseous involvement is injury which occurs to the small vasculature of the Haversian canals and the periosteal tissue. Fortunately, osteonecrosis is a relatively uncommon complication, with an incidence ranging from less than two percent to as high as 10%. This range in incidence varies with total dose administered to the mandible. (i.e. greater than 70 Gy yielding the larger number) In 95% of cases ORN is associated with soft tissue necrosis and subsequent bone exposure. Mandibles are more affected than maxillas and patients with their natural teeth have greater chances of developing ORN. Spontaneous bone exposure occurs approximately one year after finishing radiotherapy and the risk of developing this complication remains indefinitely. Osteoradionecrosis is a serious and typically late complication following radiation therapy to the head and neck, whereby irradiated bone is exposed and undergoes necrosis.⁶

Certainly one of the most devastating complication of radiation therapy to the head and neck is the development of osteonecrosis of the mandible. Another compounding factor is location of the primary tumor. If the lesion is large and is situated at the floor of mouth the rate of osteonecrosis more than doubles to 25%.⁽⁵⁾ Due to the decrease in healing capacity of the tissues from decreases in blood supply, infections to the jaw are devastating. The major etiologies are extraction of failed dentition after radiation therapy. Therefore, posterior mandibular teeth may be planned for extraction if more than 6,000 rads are expected in that field.

Great importance should be placed on pretreatment evaluation of all remaining dentition. Any questionable teeth that cannot be adequately maintained for years should be extracted. A period of two weeks prior to radiation therapy is advised for adequate healing of extraction sites. All preprosthetic surgery required, should be performed prior to the initiation of radiation therapy.⁶

Soft Tissue Necrosis

Due to excessive doses delivered to the tissues via interstitial implants or secondary to soft tissue irritation from an inadequate fitting prosthesis the soft tissue necrosis occurs. If the patient can tolerate being edentulous, it is recommended for the first six months post-therapy to allow for adequate healing and remodeling of bone. Occasionally administration of hyperbaric oxygen and antibiotics are required to alleviate the necrotic tissue.⁵

Trismus

Trismus occurs due to fibrosis in the muscles of mastication after being within the field of radiation. The management is to encourage physical therapy during and after the radiation therapy with concomitant maintenance of oral hygiene for adequate mouth opening for proper dental care.⁷

Abnormal Development of the Dentition

Tooth development begins at four months in utero and continues until early adolescence when the permanent teeth complete their formation. As with many other tissues, radiation has the potential to interfere with normal growth and maturation of the developing dentition. The severity of malformation is dependent on the stage of development at which the teeth are irradiated and the total dose received. Abnormal development in humans has been observed with a total dose as low as 400 cGy.¹ Dental abnormalities include crown and root dwarfism, root shortening, incomplete calcification, abnormal curvature of the roots, delayed or arrested eruption, and ankylosis of primary teeth. Shortened roots may lead to inadequate anchorage of the teeth in the supporting bone with subsequent loosening, increased susceptibility and involvement with periodontal disease, and early tooth loss. Ankylosis of primary teeth as well as delayed or abnormal eruption of permanent teeth may lead to significant malocclusion. These problems may require substantial efforts by the general dentist in conjunction with other specialists to restore adequate form and function to the dentition.⁸

Abnormal Facial Development

In the same vein as disturbed dental development, the structures of the facial complex, which are also actively developing in the child, may also be adversely affected by radiation therapy. These changes are secondary to radiation effects on cartilagenous growth centers. These areas are located, for the mandible, in the condyles, and for the maxilla, in the sutural growth centers. Higher radiation doses on the order of 6000-7000 cGy are associated with disturbances of facial growth and associated malformations. The child with these growth disturbances may develop micrognathia, maxillary deficiency, retrognathia, skeletal and dental malocclusion as well as other abnormalities in the facial complex. The management of those long term survivors who manifest these complications involves a team approach involving the dentist, orthodontist, oral and maxillofacial surgeon.⁸

Radiation caries

Changes in the chemical composition of saliva and increased amounts of cariogenic oral bacteria result in rapid decalcification of dental enamel. Radiation caries is not caused directly by irradiation, but results from the sequelae of xerostomia: decrease of pH, reduced buffering capacity, and increased viscosity.⁹ Clinically it has a rampant form, and tends to spread to all dental surfaces, changing their translucency and color. The carious process can cause increased friability and the breakdown of teeth. The most common type is widespread superficial lesions attacking buccal, occlusal, incisal and palatal surfaces.¹⁰

The craniofacial disturbances are those that shall occur when radiation therapy is performed in children. This way, irradiation may induce some disturbances in the craniofacial region, if it is performed in earlier stages, when teeth are still being formed.

Abnormally small teeth (microdontia), short or blunted roots, small crowns, malocclusion, incomplete calcification, enlarged pulp chambers (taurodontism), premature closure of apices and delayed or arrested development of teeth have been reported.^{11,12} The occurrence of these changes in the primary teeth can cause significant malocclusion and may adversely affect facial development.⁹ Children undergoing radiation therapy may experience abnormalities in the growth and maturation of craniofacial skeletal structures. Craniofacial and dental abnormalities can cause severe cosmetic or functional sequelae, necessitating surgical or orthodontic intervention.^{13,14}

Dysgeusia

Dysgeusia affects patients from the second or third week of radiotherapy onwards, and it may last for several weeks or even months. It occurs because the taste buds are radiosensitive, with the degeneration of their normal histological architecture. The increase of salivary flow viscosity and the saliva biochemical alteration creates a mechanical barrier of saliva which makes it difficult the physical contact between the tongue and foodstuff. The recovery until reaching almost normal levels generally takes place around 60 to 120 days after the end of the radiation. Studies show that dysgeusia is a complaint by approximately 70% of patients submitted to radiotherapy, also implying in the loss of appetite and weight, being the most uncomfortable complication for most radiated patients.^{15, 16, 17}

Effects of Surgical Treatments

The factors that influence the choice of a particular surgical approach for primary tumors of the oral cavity are the size of the primary tumor, its depth of infiltration, the site of the primary tumor (that is anterior versus posterior location), and proximity of the tumor to mandible or maxilla.¹⁸ The most commonly employed surgical approaches for resection of primary oral cancer are perioral, mandibulotomy, lower cheek flap approach, visor flap approach or upper cheek flap approach. The visor flap avoids a lower lip splitting incision and provides satisfactory exposure only for the anterior aspect of the oral cavity. It, however, produces numbness of the skin of the chin due to the necessity to divide both mental nerves. Similarly, a sublabial degloving approach avoids an upper lip splitting Weber-Ferguson incision for resection of tumors of the anterior part of the nasal cavity and the infrastructure of the maxilla.¹⁹

Speech and swallowing

Surgical resection of cancers in the oral cavity impacts on the two most important functions of the organs involved: speech and swallowing. More specifically, the oral preparatory phase (formation of a bolus) and the oral phase of normal deglutition, can be significantly impaired following tumour ablation. Loss of a significant portion of the tongue will limit the ability to transfer food into the appropriate position for grinding by the dentition. Therefore, the first phase of swallowing is disrupted. The transfer of the bolus from the anterior portion of the oral cavity to the area of the tonsillar pillars, where the initiation of

the swallowing reflex occurs, constitutes the second phase of swallowing. The harmonious coordination of the lips, tongue, buccal mucosa and maxillomandibular complex is required for completion of these phases and progression to the pharyngeal phases of swallowing. The same structures are associated with speech production and more specifically articulation.²⁰ As a general rule, ablative surgery that involves the most anterior portion of the oral tongue is associated with significantly altered speech, while resections that incorporate the posterior tongue affect swallowing. As postsurgical time progresses, surgical site scarring and fibrosis, along with xerostomia from adjunctive radiotherapy, further impairs speech and swallowing. The complexity of the function of the oral cavity structures cannot always be restored to their presurgical status despite use of swallowing manoeuvres and sensate free tissue transfer. Difficulties with articulation, chewing and swallowing could become long-term problems for these patients, and adequate rehabilitation and support should be initiated early. Consultations with speech and swallowing services are imperative in assisting the patient to regain their pretreatment status and possibly avoid long-term dependence on gastric tubes, recurrent aspiration, and communication difficulties.^{21, 22}

Masticatory function and nutrition

Masticatory function is adversely influenced by the surgical management of oral cancer. The tongue, floor of mouth, maxilla and mandible with the adjacent tissues are vital structures used for mastication and their anatomic and functional integrity is altered during ablative surgery. For efficient mastication all three components of mastication (manipulation, trituration, and consolidation) are required, and are the result of synchronous interaction of hard and soft tissues.²³ Mandibular or maxillary resection affects the grinding ability either due to loss of stable and reproducible stomatognathic system relationships or due to loss of tooth-to-tooth contacts and diminished biting forces. In addition, loss of soft tissue bulk and sensation causes difficulties with the patient's ability to manipulate the food bolus to the occlusal table, retrieve the bolus, and then consolidate it prior to deglutition. Numerous studies have evaluated the limitations associated with mastication status post cancer resection and the effects of reconstruction on masticatory function. Biting force testing, and those evaluating the tongue and cheek function, could be employed to evaluate the specific aspects of mastication. In addition patient questionnaires are used to access the overall efficiency in masticating food and the quality of life following mandibular resection with respect to success of reconstruction utilization. Unfortunately, significant variability in the testing instruments utilized in these studies, has resulted in conflicting results and conclusions.^{24, 25} It is universally accepted that reconstruction of defects in the oral cavity, at the minimum results in decreased scar formation and reduced associated functional and cosmetic limitations. Soft tissue reconstruction with a pedicle flaps and the use of reconstruction plates to span bony continuity defects has been shown to be superior to simple closure techniques alone. With the availability of free tissue transfer, composite flaps can restore not only tissue bulk and facial aesthetics, but address masticatory function due to the potential for future dental rehabilitation.^{26,27} Limited interocclusal opening, less than 35 mm between the maxillary and mandibular incisors, is one

cause of trismus based on the restrictions in mouth opening and mandibular function perceived by the patients. Trismus (restricted mouth opening) is a common complaint following oral cancer surgery. Fibrosis and scar contraction, in addition to contraction of the muscles of mastication, are the main reasons for inability of the patient to open the mouth. Common oral cancer procedures resulting in trismus include maxillary surgery involving the origin of the medial and lateral pterygoid muscles from the pterygoid plates, or mandibulectomy procedures involving any of the muscles of mastication, including the temporal muscle insertion to the coronoid process, the masseter muscle insertion to the mandibular angle and ramus, and the pterygoid insertions to the medial ramus and condylar neck. Of course, adjuvant radiotherapy may lead to fibrotic changes which may exacerbate the magnitude of surgically-induced trismus. Finally, disarticulation of the temporomandibular joint for tumour eradication will certainly lead to similar limited mouth opening. Exercise regimens, and mouth opening assisting devices, either active or passive, are regularly prescribed to assist these patients. Unfortunately, if these steps are not incorporated early, before severe scarring has occurred, and maintained long-term, only limited improvement in trismus can be expected.^{28, 29} As a result, the presence of these difficulties with mastication, swallowing, trismus, along with utilization of bulky tissue for coverage of defects that do not always address the functional needs of the cancer patient all contribute to limitations in food intake and compromise the nutritional status of patients. A significant number of these patients are forced to adapt specific diet modifications that may lead to nutritional deficits. The usual problems are inadequate protein intake and frequent episodes of dehydration, and some patients become dependent on feeding formulas through gastric tubes. Although these formulations are appropriately balanced with adequate calories, issues of intolerance, diarrhea, dehydration and electrolyte imbalance are very common. Nutritional education and support, along with close monitoring of the caloric and nutritional intake of these patients, will assist in preventing long-term deficits and frequent hospital admissions.^{30,31} Additionally, the patient population with oral cancer may have a social history significant for alcohol abuse, and preexisting nutritional deficiencies, and this may impact on continued malnutrition as well as poor wound healing postoperatively.

Cancer resection: neurologic complications

Several cranial nerves are at risk during resection of primary tumours as well as neck dissection for removal of "at risk" or involved lymph nodes. Tumour size and location as well as the extent of neck disease if present, often necessitate cranial nerves directly involved or in close proximity to be sacrificed. Furthermore the approaches often required to access and ensure adequate tumour resection can endanger integrity of the cranial nerves in the vicinity.

Cranial Nerves at risk for postsurgery dysfunction Spinal accessory nerve

There are several nerves at risk for iatrogenic injury during extirpative surgery in the head and neck due to their anatomic proximity to the surgical field, especially when the surgery involves neck dissection. Nodal metastasis has long been considered an ominous sign in head and neck cancer, and

radical resection of the cervical lymph nodes, with adjacent muscles, vessels and nerves was advocated. This was based upon the same principles applied in breast cancer surgery, and it was considered the primary method of managing this disease process. This type of radical surgery was accompanied by serious postoperative functional and aesthetic complications. Shoulder pain and spinal accessory nerve dysfunction are reasons to that have led surgeons to consider less aggressive surgical techniques to manage cervical nodal metastasis in the head and neck cancer patient. Nerve preservation is not synonymous with nerve function preservation, and "shoulder syndrome" can develop even when the spinal accessory nerve is not sacrificed. Pain, muscle weakness, shoulder movement restraint, deformity and inability to abduct the upper extremity above 90 degrees are the results of denervation of the trapezius muscle. Transection of the eleventh cranial nerve during radical surgery, or excessive manipulation during less radical procedures, as well as severing the anastomosis with the cervical plexus, may all result in this complication. Some debate exists in the literature regarding the actual incidence of developing shoulder syndrome even after preserving the spinal accessory nerve. All studies have clearly demonstrated that when the nerve trunk and its anastomosis with the cervical plexus are preserved, patients have better postoperative function and significantly less pain and deformity. Careful dissection around the vicinity of the nerve, limited use of electrocautery, and early identification based on known anatomical landmarks, may help to limit surgically-induced neural trauma. Direct primary anastomosis of the iatrogenically severed nerve is possible, and has been described in the literature, however, there are no available techniques to restore the aesthetic component of "shoulder syndrome", but aggressive immediate physical therapy can improve functional outcomes.^{32,33,34}

Marginal mandibular branch of the facial nerve

The marginal mandibular branch of the facial nerve (C.N. VII) is at risk during incision and elevation of the flaps for standard neck dissections, and access to the oral cavity for composite resections. The nerve runs at the under surface of the platysma muscle and is superficial to the facial vein at the submandibular gland region.³⁵ Dingman and Grabb in 1962 have described the anatomic location of this nerve, with a position superior to the inferior border of the mandible in 81% of cadavers proximal to the facial vessels, and in 100% of specimens distal to the facial vessels. On occasion, it may be more hazardous to dissect and mobilize the nerve so that the facial vein can be used to retract it away from the surgical field. Nodal dissection around the facial vessel, however, is not compromised with this surgical manoeuvre. Injury to this nerve causes alteration of the mobility of the corner of the mouth due to disruption of the innervation to the orbicularis oris and depressor anguli oris muscles. In addition to the functional disturbance, transection of this branch has adverse cosmetic consequences. Inability to control the movement of the lower lip can interfere with liquid consumption, and gives the patient the appearance of having sustained an injury similar to a cerebrovascular accident.³²

Hypoglossal and lingual nerves

The hypoglossal nerve (C.N. XII) provides motor innervation to the ipsilateral tongue, and the lingual nerve (C.N. V3)

provides sensation and taste innervation, via the chorda tympani branch of the facial nerve (C.N. VII), to the anterior 2/3 of the ipsilateral tongue. Both nerves may be injured iatrogenically during neck dissection, and excision of the tongue and floor of mouth may further endanger the lingual nerve. Unless there is gross neural invasion by the cancer, or the path of the nerve runs directly through the tumour, both nerves are usually preserved. Hypoglossal nerve dysfunction can present with subclinical symptoms with deviation of the tongue to the ipsilateral side of injury, accidental tongue biting, and dysarthria. Patients may also experience an exaggeration of their difficulties with mastication and deglutition that are already present following surgery. In cases of bilateral hypoglossal nerve injury, upper airway obstruction can occur when the patient is placed in a supine position. Additionally, atrophy of the muscles of the tongue can occur and add to the functional difficulties experienced by these patients.

Right hypoglossal nerve dysfunction

Ipsilateral loss of sensation to the tongue from lingual nerve injury can further impact on the difficulties with mastication, speech, swallowing and injury to the tongue during speech and mastication. These injuries can occur from traction or dissection around the lingual nerve during surgery, and may not always be recognized until later in the postoperative course. A compromised ability to taste foods due to chorda tympani nerve injury may also contribute to decreased food intake and malnutrition. Rehabilitation for speech and swallowing, using physical therapy is usually beneficial for these patients.^{32,36}

Vagus, recurrent laryngeal and superior laryngeal nerves

Direct or indirect injury to the vagus nerve or its branches, specifically the recurrent and superior laryngeal nerves, can occur during dissection around the carotid sheath. mostly due to the traction on the main trunk of the nerve, or lack of identification of the nerve during neck dissection, or placement of haemostatic clips to control haemorrhage during surgery. This is Unilateral true vocal cord paralysis, in the median or paramedian position, is the result of injury to the recurrent laryngeal nerve, and is generally well tolerated due to compensation from the intact contralateral vocal cord. However, mild to moderate hoarseness and diminished cough efforts are commonly experienced by patients. This problem becomes even more concerning in cases of bilateral injury when upper airway obstruction may result. Injury to the branches of the superior laryngeal nerve can occur during dissection around the superior thyroid branch of the external carotid artery. This may result in minor swallowing difficulties due to decreased sensation at the laryngeal inlet, or decreased tensor capability of the true vocal cord. Early fatigability and decreased ability to phonate high pitched sounds may seriously affect professional vocalists or public speakers. Direct laryngoscopy alone, or in combination with motor speech evaluation, and a high index of suspicion, can all assist in the accurate diagnosis of these neurologic injuries. Prevention remains the best management, and patients who depend on their voice professionally, require a detailed consultation and evaluation before and after surgery.³⁷

Sympathetic trunk

Disruption of the sympathetic trunk nerve fibers may lead to ipsilateral Horner's syndrome. This is usually due to a surgical

dissection that extends too far medially behind the carotid sheath. Horner's syndrome involves blepharoptosis due to disruption of the innervation to Mueller's muscle, miosis or pupillary constriction, anhidrosis with lack of perspiration of the forehead skin, apparent enophthalmos, and vascular dilation ipsilateral to the injury. Although the physical findings are pathognomonic for the diagnosis of Horner's syndrome, the clinical presentation can be occult and often variable. In addition, since Horner's syndrome findings may be due to variety of other factors, such as metastasis or vascular injuries, early recognition is of high importance.^{32,36}

CONCLUSIONS

The early complications associated with oncologic surgery for oral cancer are the similar to other surgical procedures. The potential long-term complications however are quite challenging for the oncologic team as well as the patient who survive oral cancer, primarily due to the highly specialized regional tissues involved in the surgical field. Hence it is of paramount importance to recognize and avoid those potential complications life by strict adherence to basic surgical principles and in depth knowledge of the complex regional anatomy in order to improve the quality of life for the cancer patients.

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