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ARTICLE

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Pentoxifylline and tocopherol for prevention of osteoradionecrosis in patients who underwent oral surgery: A clinical audit

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Abstract

Purpose: Osteoradionecrosis (ORN) of the jaw is a severe and debilitating complication of the head and neck radiotherapy which frequently occurrs after oral surgery. This clinical audit aims aevaluate the effectiveness of combined use of pentoxifylline and tocopherol (PENTO) in prevention ORN onset in patient who underwent oral surgery after head and neck radiotherapy (RT).

Material method: In this clinical audit Pentoxifylline 400 mg, twice a day, and Tocopherol 800 IU once a day (PENTO protocol) have been prescribed. Patients started the protocol 1 week before the surgical procedure and continued for 8 weeks after.

Results: Twenty-nine patients were included. They received 75 surgical interventions under PENTO protocol: 71 surgical procedures of dental extraction (single or multiple dental extractions in each session) and four implant placements. A total of 152 dental extractions were carried out: 64 surgical extractions which required the raising of mucoperiosteal flap, and 88 simple extractions. Four out of 29 patients developed ORN after surgical procedures: four cases of ORN occurred after dental extractions (5.6%) and one case of ORN after implant placement (25%).

Conclusion: PENTO is a useful ORN preventive protocol, low-cost and clinically feasible, safe and well tolerated by patients. Further studies should focus on better defining the effectiveness PENTO, independently from the antibiotic therapy.

KEYWORDS
head & neck radiotherapy, ORN prophylaxis, osteoradionecrosis, pentoxifylline, tocopherol

1 | INTRODUCTION

Osteoradionecrosis (ORN) of the jaw is one of the most severe and debilitating complications of the head and neck radiotherapy (RT).[1,2] ORN incidence ranges from 2% to 22% and, in the 70% of cases, ORN occur within 3 years after RT.[3,4] The most frequent trigger event is the dental extraction, although denture-related chronic trauma, odontogenic infections and dental implantology can also be associated to the ORN onset.[4]

ORN pathogenesis has been related to the "pathophysiological triad" represented by hypoxia, hypovascularization, and hypocellularity,[5] where the radiations induce a vascular thrombosis with consequent hypoxia and cell death, relegating bacteria only to a role of contaminants.[6] Hyperbaric oxygen (HBO) was, thus, proposed for ORN treatment, although it is not easily accessible in all clinical settings, it is expensive and it has contraindications for patients suffering from pulmonary emphysema, heart disease, past history of thoracic surgery, active cancer, and barotraumatic otitis.[7]

Other treatments, such as laser therapy and ozone therapy, have been proposed for the management of ORN. Ozone delivered as oil suspension has been used in topical applications on the exposed bone for 10 min. The application was repeated each week until movement of the necrotic fragment was noted (3–19 ozone applications).[8] Low-level laser therapy (LLLT) and antimicrobial photodynamic therapy (aPDT) have been used for the management of ORN with the aim of stimulating the affected area towards homeostasis and to promote the healing of the oral mucosa.[9]

A further theory is represented by the "radiation-induced fibrosis" (RIF) theory for ORN pathogenesis, proposed by Delanian,[10] which led to the proposal of an anti-fibrosis and anti-oxidation protocol for the treatment of ORN, based on the combined use of pentoxifylline and tocopherol (PENTO).

Pentoxifylline is a methylxanthine derivative used for the treatment of vascular disorders, able to increase microvascular perfusion and to act against some inflammatory mediators, including TNF-α.[11] Pentoxifylline exerts an inhibition of the inflammatory reaction in vivo and increases the activity of collagenases.[6] Tocopherol is a methylated phenolic compound that is part of vitamin E group, and it acts as anti-oxidant. In combination with pentoxifylline, a positive synergistic effect on the progression of fibrotic and inflammatory lesions, originating from RT treatment, has been shown.[11] Literature supports PENTO as pharmacological therapy in the management of ORN and of medication-related osteonecrosis of the jaw (MRONJ), in order to gradually isolate bone sequestration and to facilitate the following surgical phase.[12,13] PENTO has also been proposed as prophylactic therapy for ORN in patients who underwent head and neck RT and need oral surgery procedures,[4] although no standard of care is currently available.[6] Since data regarding the clinical efficacy of PENTO for ORN prevention are still poor and heterogeneous,[4,14] the aim of this paper is to evaluate the prophylactic effectiveness of PENTO in preventing ORN after minor oral surgery and to propose a prognostic score useful for the ORN risk analysis of the single patient.

2 | MATERIAL AND METHODS

This clinical audit evaluated with a retrospective analysis the effectiveness of PENTO-protocol in ORN prevention after oral surgery in a cohort of patients who previously underwent head and neck RT and were referred to our hospital from 2011 to 2018. Information regarding patients undergoing RT of the head and neck area was collected in a dedicated archive, consulted to identify patients who have received dental extractions or dental placements. PENTO is the therapy currently in use in clinical practice for the prevention of ORN, as supported by previous literature and considering the clinical feasibility.[4,14,15] Since ORN is a not rare complication in the absence of preventive measures, it is not ethically acceptable to plan an intervention study that included, in the comparison group, non-therapy or placebo. Exclusion criteria were patient's therapy with bone-antiresorptive and/or antiangiogenic drugs associated to MRONJ. Patients who did not strictly comply with the PENTO-protocol were excluded.

2.1 | ORN definition and diagnosis

ORN is defined as an area of exposed necrotic bone in the maxillofacial area, lasting for at least 3 months with no evidence of clinical healing, in patient who underwent RT of the head and neck and in absence of local neoplastic recurrence or metastatic disease.[5,16–18] If a bone exposure occurred, but it was completely re-epithelialized in a period of time shorter than 3 months, it was classified as delayed healing.

2.2 | PENTO protocol

Prophylactic PENTO-protocol included the administration of pentoxifylline 400 mg, twice a day, and tocopherol 800 IU once a day. The original protocol proposed by Lyon et al. considered the administration of tocopherol 1000 IU per day.[15] However, in Italy, tocopherol is not available in

TABLE 1 Prognostic score used to classify risk of ORN onset

Prognostic score for ORN onset*			
Age	+1 if > 65 years old	+2 if > 75 years old	
Chemotherapy	+3 if underwent chemotherapy	+0 if not	
Dental implantology	+3 if underwent implantology	+0 if not	
Number of dental extractions (n)	+1 if n < 5	+3 if 5 < n < 10	+5 if n > 10
Level of oral hygiene	+0 if good	+1 if moderate	+2 if low
Scores 0–4: low risk			
Scores 5–7: moderate risk			
Score ≥8: high risk			

*Dose radiation was not considered since this data was available only in 12 out of 29 patients.

capsule of 500 IU, but only in capsule of 400 IU; for this reason, the dosage was modified from 1000 IU to 800 IU per day. Patients should start the PENTO protocol 1 week before the surgical procedure and should continue for 8 weeks after.[15,19] Professional oral hygiene scaling was also carried out during the 2 weeks prior the surgery. Antibiotic therapy was prescribed, starting from the day of surgery, in all cases of clinical infection and in all cases of implantology. Local antiseptic therapy (chlorhexidine 0.2% mouthwash and/or 1% gel) was prescribed for 7–14 days after the surgery.

Each patient was evaluated by a multidisciplinary team that also included oncologists, before starting PENTO protocol, to exclude contraindications for performing the PENTO protocol.

Patients, who reported side effects while taking PENTO, should interrupt immediately the drug intake. Patients who did not fully adhere to the PENTO protocol were excluded from this clinical audit.

2.3 | Surgical procedures

The included surgical procedures were tooth extractions and dental implant placements. We defined as "intervention" a single surgical session in which one or more surgical treatments were performed involving one or more quadrants of the mouth; we evaluated the ORN onset for each singular area of treatment. Tooth extractions were performed minimizing trauma on the hard and soft tissues, post-extraction sockets were closed by primary intention. When multiple extractions were necessary, a maximum of six teeth were extracted during the same procedure. Implantology was performed with a two-stage approach and the healing screws were placed after at least 3 months. The following data were also collected: site of the primary tumor, systemic diseases, current or previous pharmacological therapies, RT total dosage, time elapsed between surgery and RT, previous ORN and type of surgical procedure performed.

2.4 | ORN prognostic score

To evaluate the patient's risk of ORN development, a prognostic score, based on age, chemotherapy, type of intervention and oral hygiene was investigated. According to this prognostic score, reported in Table 1, patients were divided into three groups of risk (low, moderate, high) (Table 1). This prognostic score could represent a useful tool during the preoperative phase for evaluating the risk of ORN onset in patients who underwent head and neck RT and need oral surgery treatments.

2.5 | Statistical analysis

Sample size calculation was based on results from previously available literature.[20,21] Since the primary outcome was to verify the number of patients who have developed ORN after surgery under PENTO, it was estimated to include at least 40 patients, after having performed the analysis of the available historical series through the clinical unit's medical records. Descriptive statistics included means and standard deviations for continuous data and percentages for categorical data. The *t*-test was used to compare the mean values of continuous variables. Statistical significance was considered for $p \leq .05$.

3 | RESULTS

A total of 75 surgical interventions were performed on 29 patients, including 18 men (62%) and 11 women (38%), with an average age of 66.52 ± 13.63 years (range: 35–89 years). They included 71 surgical extractive procedures (during each surgical sessions were performed single or multiple dental extractions) and four implant placements. One-hundred fifty-two dental extractions were carried out: 64 surgical extractions required raising mucoperiosteal flap, while 88 were simple dental extractions. The

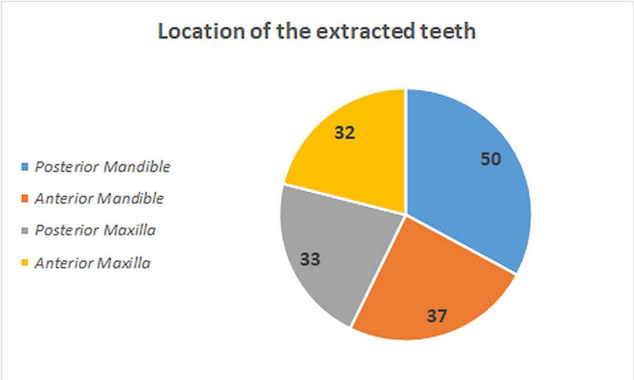

FIGURE 1 Numbers of the extracted teeth according to the different locations in the oral cavity [Color figure can be viewed at wileyonlinelibrary.com]

extracted teeth were 50 (32.9%) in the posterior mandible, 37 (24.3%) in the anterior mandible, 33 (21.7%) in the posterior maxilla and 32 (21.1%) in the anterior maxilla (Figure 1). The average number of extracted teeth per patient was 5.24, with a maximum number of 23 (performed in five different surgical sessions) and a minimum of 1. Nine dental implants were placed: five in the posterior mandible, two in the anterior mandible, and two in the premaxilla.

The primary tumors was localized in the oral cavity in 17 cases (58.7%), the pharynx in 4 (13.8%), the larynx in 3 (10.4%), the thyroid in 2 (6.9%), the nose in 1 (3.4%), the cervical area (lymphoma) in 1 (3.4%) and the submandibular area (metastasis from unknown primary tumor) in 1 (3.4%).

The cumulative dose of radiation was available only for 12 out of 29 patients, in the other cases, the radiant dose was unknown. In these 12 cases, the mean dose administered was 59.5 Gy and, in five cases, exceeded 60 Gy; in three cases it corresponded to 60 Gy and in four cases it was less than 60 Gy.

The average time elapsed between the end of RT and the surgical intervention was 42.13 ± 44.36 months (range: 4–180 months), as calculated on 23 patients, since in six cases the data regarding RT were not available. Most patients ($n = 19$, 82.6%) required oral surgery procedures between 6 months and 5 years after RT.

In our audit, 13 (44.8%) out of 29 patients underwent chemotherapy in addition to RT. Moreover, 5 (17.2%) were affected by diabetes mellitus, 8 (27.6%) by arterial hypertension and 1 (3.4%) by osteoporosis.

Twenty-eight patients underwent dental extractions, while one patient underwent only implantology. Thirteen of them received post-operative antibiotics therapy in association with the PENTO protocol, in particular amoxicillin 1 g, three times daily for 2 weeks or clindamycin 600 mg three times daily in cases of allergy to penicillin. Antibiotics therapy was post-operatively given in all procedures of dental implantology (amoxicillin 1 g three times daily, for 6 days).

TABLE 2 Different risks of develop ORN in the study population according to the prognostic score

Risk of ORN onset	Number of patients
High	7
Moderate	13
Low	9

Patients were divided in different groups according to the different risk of developing ORN (Table 2). The mean value obtained for our prognostic score was 5.82 (moderate risk). The average follow-up after the last surgical intervention was 17.86 ± 18.04 months (range: 2–69 months), while the average follow-up period was 29.41 ± 22.57 months (ranging from 2 to 78 months). At the examinations at second months from surgery, four patients showed excellent clinical healing with complete socket re-epithelization without any signs of bone exposure, but they missed the following follow-up visits.

In this work, four patients out 29 (13.8%) developed ORN after surgical procedures (four males; mean age: 75.7 ± 10.5 years): four after surgical dental extractions (1/71; 5.6%) and one after dental implant placement (1/4; 25%) (Table 3). In all cases, ORN was localized at the mandible, but in one patient it involved both the mandible and the right posterior maxilla. Three out of four patients underwent previous chemotherapy, two were affected by diabetes mellitus, one by hypertension and one by osteoporosis. In three out of four patients, the primary tumor was localized in the oral cavity, while in one case in the larynx. The four patients who developed ORN showed an increased timespan from RT to dental surgery (55.5 months ± 60.27) in comparison to the patients who did not develop ORN (39.32 months ± 41.86), but this association was not statistically significant (Figure 2). Three of the patients affected by ORN were in the high-risk group and one was in the moderate-risk group and, consistently, the group of patients who developed ORN showed a statistically significant higher value of the prognostic score (8.75 ± 2.98) compared to patients who didn't develop the complication (5.36 ± 2.10) (t-test, $p = .01$) (Figure 3).

Considering ORN management, two patients received a conservative surgical intervention. Mandibular resection was required in one case and, in the other remaining patient, only a periodical follow-up of the exposed necrotic area was performed considering the clinical stability and asymptomaticity.

TABLE 3 Patients who developed ORN after surgical procedures

	Patient 2	Patient 11	Patient 14	Patient 25
Age	89	78	64	72
Chemotherapy	No	Yes	Yes	Yes
Risk of ORN	Moderate	High	High	High
Localization	Mandible	Mandible	Mandible and Maxilla	Mandible
Surgical Procedure	Dental extractions	Dental extractions	Dental extractions	Implantology

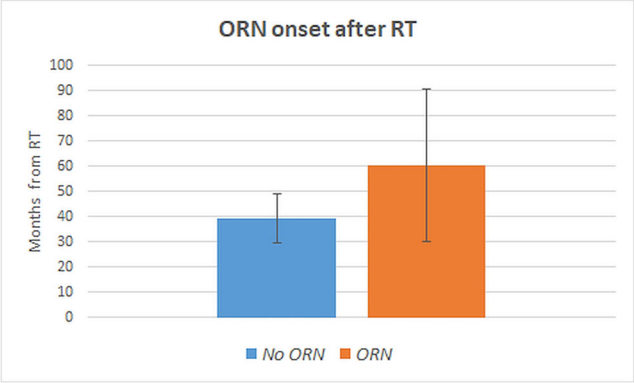

FIGURE 2 ORN development correlated with the timespan (months) from RT [Color figure can be viewed at wileyonlinelibrary.com]

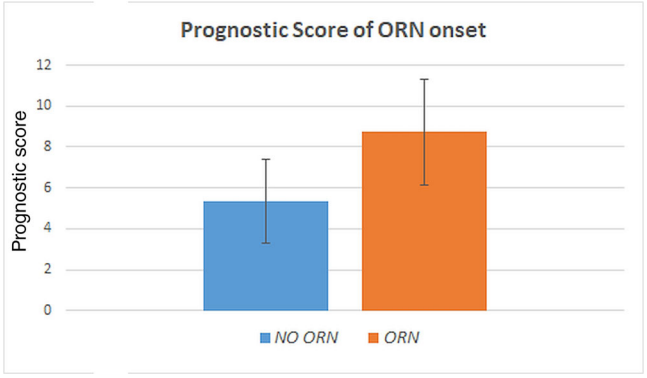

FIGURE 3 Prognostic score to assess the risk of ORN onset after oral surgery procedures, comparing patients who developed or not the complication [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

PENTO as pharmacological antioxidant therapy has been reported to induce radiation-induced fibrosis regression.[4,16,22] ORN usually does not show tendency to spontaneous resolution,[17] but gradually worsens in association with further complications such as extra-oral fistulae, ulceration of overlying skin, facial deformities, pathological bone fractures and even sepsis.[17]

ORN incidence seems to be similar in both gender with a male/female ratio of 1.6:1, while the mean age at onset is 50–60 years.[16,23] The mandible, due to its higher bone density, is the most common oral site affected by ORN onset.[16] In our clinical audit, all ORN cases occurred in male patients and involved the mandible; one patient developed ORN also in the maxilla. The mean age at onset was of 75.7 years.

The incidence of ORN in our work was four out of 29 patients: four out of 71 (5.6%) surgical extractive procedures and one out of four (25%) implant placement. The largest retrospective study, evaluating 830 patients over a period of 30 years, reported an incidence of ORN of 8.2% independently from oral surgery treatments, while a more recent systematic review estimated an overall incidence of 7%.[19,24] The risk of ORN is lifelong,[16,25] but some Authors suggest that, in 70% of cases, it occurs within 3-years after RT, with a peak between 6 months and 2 years after RT.[3,16,22,26] On the contrary, a systematic review reported the risk of ORN increasing over time from 8% at 1 year after RT to 16% at 2 years,[19] and other Authors confirmed that ORN risk tends to increase through lifespan.[4] Our findings are consistent with these data, since patients, who developed ORN, underwent oral surgery after a higher timespan from RT than patients who did not develop ORN (mean time lapse of 55.5 vs. 39.32 months, respectively). Our data, in particular, included a case of mandibular ORN, which occurred after the extraction of the second molar, in a patient who received the head and neck RT 12 years (144 months) before the intervention.

Many studies reported the efficacy of PENTO in the treatment of ORN, but very few data are available about its clinical administration in prophylactic protocols. Patel et al. retrospectively analyzed data on 82 patients who underwent 390 dental extractions.[4] They included patients who had RT for head and neck cancer involving: oral cavity ($n = 20$, 24%), oropharynx ($n = 25$, 31%), hypopharynx ($n = 14$, 17%), nasopharynx ($n = 10$, 12%), and other sites ($n = 13$, 16%); pentoxifylline 400 mg twice daily and tocopherol 1000 IU daily were started 1 month before the surgery and postoperatively continued until the socket had healed [4]. Only one case of ORN out of 82 patients occurred

and a low ORN incidence (1.2%) was observed.[4,19] Seventy-seven patients (94%) received post-operatively antibiotic therapy.[4] Aggarwal et al. evaluated 450 dental extractions in 110 patients affected by primary cancer located in the oral cavity (n = 26, 23.64%), oropharynx (n = 36, 32.73%), hypopharynx (n = 17, 15.45%), nasopharynx (n = 14, 12.73%), and other sites (n = 17, 15.45%).[14] Pentoxifylline 400 mg twice daily and tocopherol 1000 IU daily were prescribed from 1 month before surgery, to be continued after the intervention until the complete socket healing.[14] Two patients out 110 developed ORN (1.8%) and antibiotics were given in all patients: only postoperatively in 70 patients (67%) and also preoperatively in 40 patients (36%).[14]

The different ORN prevalence between the current and the previous studies can be ascribed to different protocols of administration: in our protocol, PENTO was given to patients 1 week pre-operatively, according to Lyons et al.,[15] and not 1 month before as proposed by Patel et al. and Aggarwal et al.[4,14] Moreover, post-operative antibiotic therapy was here given only in 14 out of 29 patients (48%), while in the other studies almost all patients received antibiotic therapy, i.e. Patel et al. in 94% of cases and Aggarwal in 100% of cases.[4,14] Furthermore, rate of patients affected by oral cancer was significantly higher in our work (58.7%) than in Patel and Aggarwal ones, where oral cancer patients represented the 24% and 23.64%, respectively. RT targeted to the oral cavity may be considered a relevant risk factor for ORN onset. Finally, also the dosage of tocopherol, even if only slightly reduced (800 IU instead of 1000 IU) from the original dosage, may be potentially associated with an increased prevalence of ORN.

Since RIF theory has been proposed, PENTO appeared a promising and feasible preventive approach to reduce ORN after oral surgery,[3,22] as confirmed by our findings. Some authors suggested also the use of combined administration of pentoxifylline-tocopherol-clodronate (PENTOCLO) for the management of advanced stage and recurrent ORN.[16,17,27] PENTOCLO protocol involves the use of pentoxifylline 400 mg, 1 tablet, morning and evening; tocopherol 500 mg, one capsule, morning and evening; clodronate 800 mg, one tablet, morning and evening, from Monday to Friday (5 days per week); the end of treatment was decided according to the complete mucosal healing and no exposed bone.[17]

Several further protocols included antibiotic prophylaxis and hyperbaric oxygen therapy (HBOT).[4,28,29] In a systematic review, which compared effectiveness of antibiotics and HBOT, the estimated ORN incidence was 6% and 4%, respectively.[19] However, HBOT is not always feasible in the everyday clinical practice, such as high number of sessions (20–30 pre-operative and 10 post-operative), low availability of facilities, high costs and specific contraindications.[19,30] HBOT may add $10 000–$50 000 to the management costs of ORN in a patient affected by head and neck cancers;[31] HBOT for ORN management has a median cost of $16 500.[32] On the other hand, in Italy the estimated cost for PENTO protocol (1 week before surgery and 8 weeks after) is approximately 250€. Despite the low cost of PENTO protocol, however, pentoxifylline is contraindicated in case of hypersensitivity to this agent or to other methylxanthines, as well as in case of pregnancy, acute myocardial infarction or severe coronary disease and risk of increased bleeding (intracranial or retinal bleeding).

The real effectiveness of antibiotic prophylactic therapy in prevention of ORN remains controversial and still need to be better elucidated.[4,19] Moreover, there is no consensus on which antibiotic regime may be the most effective.[2]

Few side effects associated with PENTO protocol have been previously reported: gastric irritation, nausea, dyspepsia, epigastralgia, headache or vertigo, asthenia, hot flushes, disturbed vision, difficulty in swallowing and allergy.[4,14] None of the 29 patients included in this clinical audit reported side effects related to assumption of PENTO. However, considering our experience, only two patients, who were excluded from the present audit because they did not fully adhere to the PENTO protocol, reported side effects related to PENTO intake. The referred side effects were nausea, diarrhea, dizziness and asthenia and they completely resolved interrupting the drug intake.

Despite the small number of patients, our secondary aim was proposing a prognostic score useful to define the risk of ORN onset, to be assessed before oral surgery evaluating the following risk factors: age, association with chemotherapy, dental implantology, number of extracted teeth and level of oral hygiene. This score was set up considering previous studies reporting clinical, pathological and anamnestic risk factors for ORN development[16]: in particular, related to RT and other cancer therapies (RT dosage > 60 Gy; RT associated with chemotherapy; short RT regimens associated to high doses per fraction (>1.8 Gy); brachytherapy); related to the tumor (tumor stage and size (staging > T1); bone invasion or proximity); systemic diseases (hypertension, diabetes mellitus, malnutrition, immunodeficiency, connective tissue disorders, malnutrition); local factors (odontogenic infections; chronic periodontal disease; poor oral health and oral hygiene; poor prosthetic adjustment; oral surgical trauma such as in case of tooth extraction, implantology, bone biopsy; smoking and alcohol consumption).

The limitations of our clinical audit are mainly related to the retrospective design, which hindered the complete data collection, the sample size based on historical series and the lack of a control group. Furthermore, ORN preventive protocol requires patient to strictly adhere to the PENTO regimen for a long period, usually weeks/months, which

cannot be assessed with certainty. No data were available regarding confounding factors, such as tobacco use, indications for teeth extractions, radiation scheme and dosage for each subject.

5 | CONCLUSION

PENTO protocol is low-cost, clinically feasible, safe and well tolerated by patients.[33] More comprehensive studies, controlling confounding factors such as concomitant antibiotic therapy, are necessary to establish the effectiveness of PENTO in ORN prevention. Moreover, a standardized and widely accepted protocol is still necessary in order to obtain comparable results.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

Data and sample were collected under patient's informed written consent.

DATA COLLECTION AND ETHICS STATEMENT

These data were collected during a clinical audit; thus, by definition, it does not involve anything being done to patients beyond the normal clinical management. Each procedure included in this study did not deviate from the normal clinical practice, thus respecting the standard of care and the protocols previously approved and recommended.

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