INTRODUCTION

Traditionally, osseointegrated dental implants were submerged and kept load-free for 3–8 months to minimize the risk of implant failures (Brånemark et al., 1977). It would be beneficial from a patients’ perspective to reduce the healing period without jeopardizing implant success, and nowadays, immediately and early loaded implants are commonly used (Gallucci, Hamilton, Zhou, Buser, & Chen, 2018; Huynh-Ba, Oates, & Williams, 2018). Generally, in the immediate loading, the restoration is placed within one week, while in the early loading the restoration is placed between one and eight weeks (Chen, Cai, Yang, Aldhohrah, & Wang, 2019).
A recent systematic review showed no significant differences between early and immediate loading protocols in single implant crowns with regard to survival rate or marginal bone loss at 1 or 3 years (Pigozzo, Rebelo da Costa, Sesma, & Laganà, 2018). The conclusions stated in systematic reviews point out the fact that new information is needed on the medium- and long-term results of the different procedures (Esposito, Grusovin, Maghaireh, & Worthington, 2013; Pigozzo et al., 2018; Zhang, Wang, & Song, 2017).

Recently, a 10-year report from a multicenter randomized controlled trial compared immediate non-occlusal versus early loading of dental implants in partially edentulous patients using full-thickness crestal flaps at implant insertion (Zuffetti et al., 2016). In this study, there were no statistically significant differences between the two groups in term of implant/prosthesis failures, complications, peri-implant bone and soft-tissue-level change (Zuffetti et al., 2016).

Information regarding the outcome after immediate or delayed placement remains scarce, particularly with regard to flapless approach (Atieh, Payne, Duncan, de Silva, & Cullinan, 2010). A systematic review indicated that a flapless approach can be applied obtaining comparable results with respect to a conventional protocol (Lin, Chan, Bashutski, Oh, & Wang, 2014). Results on the long-term comparison of immediate versus early non-occlusal loading of conventional dental implants placed flapless in partially edentulous patients are lacking in literature (Xu et al., 2014).

The objective of this 10-year parallel group randomized clinical trial is to compare implant failures, complications, subjective satisfaction and radiographic bone level of immediate versus early non-occlusal loading of dental implants placed flapless in partially edentulous patients.

This article is reported according to the CONSORT statement for improving the quality of reports of parallel group randomized trials (Moher et al., 2010) and presents data up to 10 years after loading. Two articles presenting the data up to 1-year and 3-year follow-up have been previously published (Merli, Merli, Bernardelli, Lombardini, & Esposito, 2008; Merli, Moscatelli, Mariotti, Piemontese, & Nieri, 2012).

2 | MATERIALS AND METHODS

2.1 | Trial design

This was a mono-centre, single-blind, parallel randomized clinical trial with balanced randomization (1:1) conducted in a private clinic in Rimini (Italy) between July 2005 and November 2018. The study characteristics and technical details were described in two previous articles (Merli et al., 2008, 2012). The research was conducted in full accordence with ethical principles, including the Declaration of Helsinki, and each participant gave a written consent according to the above-mentioned principles. An independent ethics committee (Comitato Etico della Romagna, CEROM) approved the follow-up of this clinical study (Prot. 7832/2019 I.5/211).

2.2 | Participants

In summary, eligible participants were all adults, aged 18 or over, partially dentate requiring dental implants. The implant site should allow for the placement of at least one 9.5 mm long implant, and the bone thickness at the implant site had to be at least 5.5 mm. For patients with multiple areas to be restored, the operator was free at the screening visit to select one area to be included in the trial. In this area, multiple neighbouring implants could be placed.

Exclusion criteria were as follows: general contraindications to implant surgery, patients irradiated in the head and neck area within a year prior to surgery, patients with poor oral hygiene (full-mouth plaque score ≥30) and lack of motivation, uncontrolled diabetes (diabetes that is not being treated at all, or is not being adequately treated), pregnancy and lactating period, substance abusers, psychiatric problems, lack of opposing occluding dentition in the area intended for implant placement, severe bruxism or clenching, active infection or severe inflammation in the area intended for implant placement, the presence of ≤4 mm of keratinized mucosa and/or the need for bone augmentation procedures.

2.3 | Interventions

One experienced surgeon (Mauro Merli) performed all the operations, whereas patients were restored by four restorative dentists. Threaded cylindrical titanium implants (ELEMENT, Thommen Medical, Waldenburg, Switzerland) with a sand-blasted acid-etched surface were used. In some of the post-extraction sites, tapered CONTACT (Thommen Medical) implants were used. A flapless procedure was used (Merli et al., 2008, 2012). The objective was to reach
a minimum torque of 40 N cm upon implant insertion. Implants with an insertion torque of <40 N cm could be replaced by a larger diameter implant. Alternatively, the surgeon had the following options: to prepare another implant site; to leave the implant to heal unrestored for 6 weeks following the same procedures of early loading group; to heal unrestored for 6–8 months following the procedure of conventionally loaded implants; or to load the implant. An intention-to-treat analysis was used in these situations, and a per-protocol analysis was performed as a sensitivity analysis.

In general, implants were placed at the crestal level in healed edentulous ridges and 1 mm subcrestally in immediate post-extraction sockets. When a residual gap was present between the implant surface and the bone wall in the immediate extraction site, the gap was filled with Bio-Oss 0.25–1 mm granules (Geistlich Biomaterials, Wolhusen, Switzerland). No other type of bone-grafting material was used and alveolar ridge preservation was not performed. A non-submerged technique was followed.

Before abutment placement, the envelope containing the randomization code was opened, instructing the surgeon as to whether the procedure would involve immediate or early loading. Impression copings or healing abutments were placed accordingly (Merli et al., 2008).

All provisional restorations of the immediately loaded group were placed within 72 hr of implant placement. The occlusal surface of the provisional restoration was ground to avoid any occlusal contact with the opposite dentition in static and dynamic analyses.

For patients in the early loading group, restorations were placed approximately 6 weeks after implant placement. They received non-occlusally provisional fixed restorations, identical to those of the immediately loaded group.

Intra-oral radiographs of the study implant were made at implant placement, at 3 years and at 10 years of follow-up. Six months after loading, final occluding metal-porcelain prosthesis was applied. All patients were recalled every 3 months for oral hygiene maintenance and prosthetic controls up to the ten year after implant placement.

An immediate group case and an early group case are shown in Figures 1 and 2.

2.4 | Outcomes

Primary outcomes were implant failures and complications.

Outcome measures evaluated in the present study at 10-year follow-up were as follows:

Implant failure: the presence of any mobility of the individual implant and/or any situation dictating implant removal.

Any biological or prosthetic complications defined as unexpected deviations from the normal treatment outcome; examples of biological complications are haemorrhaging during and after implant placement and/or peri-implantitis. Prosthetic complications included fracture of the implant or fracture of the prosthesis.

The patient’s aesthetic and functional satisfaction was assessed by asking the patient for satisfaction on a scale from 0 to 10 where 0 meant completely dissatisfied and 10 meant completely satisfied.

Peri-implant marginal bone level: periapical intra-oral radiographs were taken with the parallel technique. The digitized radiographs were examined at 10-year by an operator (Marco Merli) blind to the group assignment. The measurer was calibrated and subjected to an intra-rater agreement test on 21 implants. The radiographic measurement was taken from the implant–abutment junction to the most coronal point of bone-to-implant contact. The measurements were made parallel to the long axis of the implant fixture and were made in pixels and converted to millimetres using the known length of the implant. Measurements of the mesial and distal crestal bone level adjacent to each implant were made to the nearest 0.01 mm. The implant was considered as a statistical unit and mesial and distal measurements were averaged.

2.5 | Sample size

The sample size calculation was performed on the number of patients likely to have at least one implant failure. From a study on partially edentulous patients, the proportion of failure in the immediately loaded group was 0.39 compared with 0.04 in the conventional loaded group (Ottoni, Oliveira, Mansini, & Cabral, 2005). A two-group continuity-corrected chi-square test with a 0.05 two-side significance level have an 80% power to detect the difference between a proportion of 0.39 and a proportion of 0.04 (odds ratio of 0.065) when the sample size in each group is of 26 patients. Thirty patients were to be included in each group to compensate for possible dropouts.

2.6 | Randomization and blinding

An investigator (M. Esposito), not involved in the selection and treatment of the patients, randomly assigned participants following simple randomization procedures (computerized random numbers) to one of two treatment groups. The randomized codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes.

Envelopes were opened sequentially only after the implants to be included in the trial were inserted, and, therefore, treatment allocation was concealed to the investigator in charge of enrolling and treating the patients included in the trial.

Although patients and the surgeon were aware of the allocated arm, radiographic outcome assessor (Marco Merli) was kept blinded to the allocation. Prosthesis failure, implant failure and complications were assessed by an independent assessor (M. Moscatelli), who was not blinded to the intervention.

2.7 | Statistical analysis

Descriptive statistics were performed using mean and standard deviations (sd) for quantitative data, and frequency and percentage for qualitative data.
In implant failure, complication and subjective satisfaction analyses, the patient was the statistical unit. Risk ratios were calculated and differences between the two groups were tested with the Fisher exact tests for implant failure and complication. For subjective satisfaction, the unpaired $t$ test was applied.

For the radiographic analysis, an intra-rater agreement was carried out. An a priori independent sample of 21 measured implant surfaces was measured twice, 2 weeks apart. A two-way intra-class correlation coefficient was calculated.

For radiographic analysis, the implant was the statistical unit. A mixed effects model was used where the patient was the random effect and the bone level at 10 years was the outcome variable. The treatment (immediate versus early loading) was the explicative variable.

Graphical residual analyses were performed to test the assumption of homoscedasticity and normality.

Significance was set at $\alpha = 0.05$. Estimates for the treatment effect, $p$-values and 95% confidence intervals were provided. The statistical software was JMP v. 13 (SAS Institute Inc, Cary, NC).

Intention-to-treat analyses were performed. Sensitivity per-protocol analyses were undertaken to compare the results obtained with the intention-to-treat analyses.

Two subanalyses considering only implants placed in immediate post-extraction socket and only implants placed in healed edentulous ridge were performed.

3 | RESULTS

3.1 | Participant flow

Sixty patients were consecutively enrolled in the trial and randomized: 30 to the immediately loaded group and 30 to the early loaded group. Three patients belonging to the immediate group and three patients belonging to the early group dropped out at 10 years. Five patients (three in the immediate group) dropped out because they refused to return to the follow-up visit, and one dropout in the early group was due to the death of the patient.

3.2 | Deviation from the protocol

Deviations from the operative protocol were described in the previous publications (Merli et al., 2008, 2012) and can be summarized.
as follows: nine implants in nine patients did not obtain the planned primary stability. Five implants were in the immediately loaded group. Two of these implants were loaded immediately with a torque of 30 N cm. Of the other three implants, one was loaded early and the other two implants were conventionally loaded (one of which was placed in a patient with two other implants that were immediately loaded). Four of the implants that did not obtain the planned primary stability were loaded early anyway, as indicated in the envelope. Two implants in two patients of the early loaded group were immediately loaded (protocol deviation) and five implants in five patients of the early loaded group were conventionally loaded because patients delayed the treatment due to work commitments (one patient), health problems (one patient), economic reasons (one patient) and due to patient’s specific personal problems that came about post surgery (two patients) (Figure 3). In addition, two patients in the immediate group refused to take X-rays at the 10-year follow-up.

3.3 | Dates of recruitment and follow-up

Patients were recruited and operated on in a private clinic from July 2005. The last 10-year follow-up was done in November 2018.

3.4 | Baseline characteristics

The main baseline patient characteristics are shown in Table 1. There were no apparent baseline imbalances between the two groups.

3.5 | Outcomes

No implant failed in the immediate group, and one implant failure occurred in the early group \( (p = 1.0 \text{ Fisher's exact test}) \). The implant failure occurred after 6 years for an implant fracture.
Three complications occurred in the immediate group and four in the early group (RR = 0.75, CI 95% 0.19 to 3.04, p = 1.0 Fisher’s exact test). In the immediate group, in two cases, the screw connecting the crown became loose and was retightened. In another case, there was a chipping of the crown. In the early group, in one case, a fistula developed 21 days after implantation, in one case mucositis developed in both the implant treated, in the other two cases the abutment screws fractured.

The two-way intra-class correlation coefficient for radiographic intra-rater agreement analysis was 0.98, considered excellent (Fleiss, 1986).

Patient’s functional satisfaction at 10-year follow-up was 9.8 (sd 0.5, 27 patients) for the immediate group and 9.6 (sd 1.0, 26 patients) for the early group. The difference between groups was 0.2 (95% CI from −0.2 to 0.7; p = .3271 t test) favouring the immediate group.

Patient’s aesthetic satisfaction at 10-year follow-up was 9.7 (sd 0.7, 27 patients) for the immediate group and 9.7 (sd 0.7, 26 patients) for the early group. The difference between groups was 0.0 (95% CI from −0.2 to 0.2; p = .9656 t test).

The mean bone level at 10 years was 0.9 (sd 0.7, 28 implants, 25 patients) mm for immediate group and 0.7 (sd 0.5, 29 implants, 26 patients) mm for early group (Table 2). The adjusted difference in bone level was 0.1 mm (CI 95% −0.2 to 0.2, p = .3752 mixed model).

### 3.6 | Sensitivity analysis

In the sensitivity per-protocol analysis, utilizing only the implants loaded in the prescribed way and visited at the 10-year follow-up (26

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**TABLE 1** Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate n = 30</th>
<th>Early n = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female patients (%)</td>
<td>20 (67)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>50.3 (28–72)</td>
<td>48.7 (19–68)</td>
</tr>
<tr>
<td>Smokers (at least 1 cigarette per day) (%)</td>
<td>3 (10)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Number of patients receiving one implant (%)</td>
<td>26 (87)</td>
<td>26 (87)</td>
</tr>
<tr>
<td>Number of patients receiving two implants (%)</td>
<td>3 (10)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Number of patients receiving three implants (%)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total number of placed implants</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Implants placed in fresh extraction socket (%)</td>
<td>13 (37)</td>
<td>16 (47)</td>
</tr>
<tr>
<td>Immediate extraction site treated with Bio-Oss (%)</td>
<td>8 (23)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Implant inserted in mandibles (%)</td>
<td>12 (34)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Implant inserted in anterior area (canine to canine) (%)</td>
<td>3 (9)</td>
<td>5 (15)</td>
</tr>
</tbody>
</table>
implants in the immediate group and 23 implants in the early group), the difference in marginal bone level was 0.1 mm (CI 95% −0.3 to 0.4; \( p = .6013 \) mixed model). The result of this analysis was substantially the same as the intention-to-treat analysis.

### Subanalyses

In the subanalysis, utilizing only the implants placed in immediate post-extraction socket and visited at the 10-year follow-up (11 implants in the immediate group and 13 implants in the early group), the difference in marginal bone level was 0.2 mm (CI 95% −0.5 to 0.8; \( p = .5553 \) mixed model).

Utilizing only the implants placed in healed edentulous ridge and visited at the 10-year follow-up (17 implants in the immediate group and 16 implants in the early group), the subanalysis showed a difference in marginal bone level of 0.2 mm (CI 95% −0.2 to 0.6; \( p = .2863 \) mixed model).

### DISCUSSION

This 10-year parallel randomized clinical trial failed to show differences between early and immediately loaded implants.

Both loading strategies achieved good clinical results, which could be maintained over a 10-year period. There was only one implant failure in the immediate group and there were three complications in the immediate group and four complications in the early group. At 10-year follow-up differences in marginal bone level were negligible, in the order of 0.1 mm. Even the subjective satisfaction was very similar between the two groups.

In this study, the immediate loading group was non-occlusally loaded within 72 hr of implant placement, while early loading group was non-occlusally loaded approximately 6 weeks after implant placement. In a recent systematic review, the immediate loading restoration was considered placed within one week while the early loaded was considered placed between one and eight weeks (Chen et al., 2019). It is important to recognize that loading after 6 weeks is not exactly the same as loading after 2–4 weeks, and this should be addressed in comparison with other study. In a beagle dog study, two different implant surfaces were used and loaded with fixed partial dentures at 2-, 4-, and 6-week post-placement (Knobloch, Larsen, Rashid, & Carr, 2004). No implant failure was observed after the 4-week time loading period. For this reason, in this study, the 6-week post-loading rationale was used.

These results are in accordance with the findings of the other published systematic review and RCTs (Esposito et al., 2013; Pigozzo et al., 2018; Zhang et al., 2017). It is likely that a significant difference in clinical and radiological outcome between these two types of loading does not exist (Atieh et al., 2010; Esposito et al., 2013).

Long-term RCT using full-thickness crestal flap at implant insertion showed no differences between immediate and early loaded dental implants (Zuffetti et al., 2016). Similar results were obtained for implants with a chemically modified SLA surface (Nicolau et al., 2018) and for short implants placed flapless (Cannizzaro et al., 2018).

In this study, only six dropouts occurred over a follow-up period of 10 years, which is a remarkable result considering the duration of the trial.

The subanalysis performed on implants placed in immediate post-extraction socket and the subanalysis of the implants placed in healed edentulous ridge confirmed the results obtained in the main analysis.

A limit to this study is represented by the deviations from the protocol. The statistical analysis of this RCT was intention-to-treat, and the data were analysed on a randomization basis (Moher et al., 2010). It is important to point out that a few patients, due to work commitments, health problems and/or financial reasons, etc., were unable to follow the designed protocol completely. A sensitivity per-protocol analysis was performed only on the implants loaded in the prescribed way with the 10-year radiographic follow-up. This evaluation confirmed the results obtained in the intention-to-treat analysis.

The sample size of this study was calculated with a power analysis based on a study in which the proportion of failure in the immediately loaded group was 0.39 (Ottoni et al., 2005). However, the incidence of failure was lower than predicted and there was

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**TABLE 2** Marginal bone level at baseline, 3 and 10 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate</th>
<th>Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone level baseline (mm)</td>
<td>3.5 (1.6)</td>
<td>3.1 (1.6)</td>
</tr>
<tr>
<td>N = 31</td>
<td>N = 31</td>
<td></td>
</tr>
<tr>
<td>Bone level 3 years (mm)</td>
<td>1.9 (0.6)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>N = 34</td>
<td>N = 31</td>
<td></td>
</tr>
<tr>
<td>Bone level 10 years (mm)</td>
<td>0.9 (0.7)</td>
<td>0.7 (0.5)</td>
</tr>
<tr>
<td>N = 28</td>
<td>N = 29</td>
<td></td>
</tr>
<tr>
<td>Bone level 10 years (mm)</td>
<td>1.0 (0.8)</td>
<td>0.9 (0.6)</td>
</tr>
<tr>
<td>Implant placed in post-extraction socket</td>
<td>N = 11</td>
<td>N = 13</td>
</tr>
<tr>
<td>Bone level 10 years (mm)</td>
<td>0.9 (0.6)</td>
<td>0.7 (0.4)</td>
</tr>
<tr>
<td>Implant placed in healed edentulous ridge</td>
<td>N = 17</td>
<td>N = 16</td>
</tr>
</tbody>
</table>

Mean and standard deviation (in parentheses).
no implant failure. In that study, the primary stability was standardized with a minimum insertion torque of 20 N cm (Ottoni et al., 2005), whereas in this study, the objective was to reach a minimum torque of 40 N cm upon implant insertion. This fact can account for the different failure implant rates between the two studies. Hence, this study could be underpowered with regard to failure of the implants. The protocol deviation could have reduced the power of the study to detect meaningful smaller clinical differences between treatments. In addition, bone level measurements were performed without a standardization stent and the length of the implant was used to “calibrate” the linear measurements. Nevertheless, different angulation of the radiograph could have produced different projection of the peri-implant bone at baseline and at 10-year follow-up.

This study was carried out in a private clinic, and the interventions were performed by an expert surgeon with 20 years of experience in implant surgery. This should be taken into consideration when extrapolating the results from this trial to other settings. Caution must be taken on the generalization of the present results since the patients attended follow-up appointments for hygiene every 3 months, which is not usual in daily practice.

In conclusion, the null hypothesis of no difference in failure rates, complications, subjective functional and aesthetic satisfaction and marginal bone level between implants that were loaded immediately or early at 10 years cannot be rejected in this randomized clinical trial. The 95% confidence intervals of the differences between the two groups were narrow and comparable for subjective functional and aesthetic satisfaction and marginal bone level; hence for these variables, the two loading treatments seem equivalent.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest in this study.

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